# Studies on Inclusion Resolution:

## Gaining insight into chemical and physical properties

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## Gaining insight into chemical and physical properties

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Wiskunde en Informatica

Proefschrift

ter verkrijging van de graad van doctor aan de Katholieke Universiteit Nijmegen,
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**Simona Müller**
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**Promotores:**

Prof. dr. A. Bruggink (KUN)

Prof. dr. B. Zwanenburg (KUN)

**Co-promotor:**

Dr. G.J.A. Ariaans (KUN)

**Manuscript commissie:**

Prof. dr. R.M.Kellogg (Syncom, RUG, Groningen)

Dr. R. Grimbergen (DSM, Geleen)

Dr. A.J.H. Klunder (KUN)

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*Die Natur ist wirklich weise:*
*Der Mensch hat zwei Ohren und eine Zunge.*
*Er sollte eben doppelt soviel hören wie reden.*

William Sommerset Maugham (1874-1965)

*(Nature is really wise:*
*man has two ears and one tongue, thus,*
*one should listen twice as much as talk.)*

Paranimfen: Sjef Cremers

Tim Detert

# Contents

# 1 Introduction

*This chapter gives a short overview of the history of inclusion complexes, describing both, the crystalline phase and interaction in solution. The basic principles of chirality and its importance are outlined. The description of the term "Inclusion Resolution" by using selected examples completes the introduction. The chapter ends with a description of the aim of research explained in this thesis and an outline of the contents.*

# 1.1 Inclusion complexes

## 1.1.1 History of inclusion complexes[8,9]

The formation of inclusion complexes is a well-known phenomenon that has been studied by several chemists throughout the years. It started from the observation that some natural objects have, because of their shapes and constructions, the capability to act as boxes for other objects. In 1849, during the development of stereochemistry, Wöhler obtained the first inclusion complex. He found quinol clathrates with hydrogen sulfide included, but at that time he was unable to explain his observation.

After van't Hoff's explanation of stereochemistry based on the tetrahedral carbon atom in 1874, molecules were given well-defined structures, so allowing a rational explanation of the inclusion process.

In 1886, Mylius made quinol clathrates that include formic acid and carbon monoxide. He concluded that there was a lack of "ordinary chemical combination" and proposed that the quinol molecules were "somehow able to lock" the guests. With these observations, Mylius took the first step towards an explanation, following a direction no one had thought of before. Nevertheless, a more exact explanation was not possible at this state of knowledge. In the following 50 years many attempts were made to find an explanation for these observations of inclusion of small molecules in the crystal lattices of larger ones.

One direction of research concentrated on the analysis of the crystal packings. By measuring the densities of crystals and a comparison with the theoretical densities of the separate molecules, it was found that the crystals are not perfectly packed, but contain some voids. An especially clear example is the difference in densities between ice and water, indicating that approximately a tenth of the total crystal volume of ice is empty space. This, however, is an exception as the densities of crystals are usually higher than those of the melts.

With the development of X-ray analyses, inclusion complexes became compounds of understandable chemical structure and behaviour. Their number and types grew quickly due to extension of the range of host compounds, both by discovering new hosts and by modification of already known ones.

## 1.1.2 Different classes of inclusion complexes[8,25]

Several types of inclusion crystals are known, e.g. those from which the guests can be removed, restored or replaced while the crystal remains unharmed. The zeolites, with their ability to loose water without breaking the crystal structure, and to take it up again, constitute the most famous example. Another type of inclusion complexes deals with some of the solvates of complex compounds, in which the guests are needed to build a stable crystal lattice. In crystallisation, the solvent may act as a kind of cement, and is hence present in the crystal.

By analysing a variety of inclusion complexes, the use of the terms host and guest appeared to be misleading. Although many inclusion complexes are known, where the host itself offers cavities for the inclusion of guest molecules, the majority of inclusion complexes is formed by a different principle. The nature of the cavities is strongly influenced by the included guest component, since the host compound itself does not contain cavities, they are created by the arrangement of host and guest in the crystal lattice, resulting in collapsing of the crystals when removing the guest compound. Crystals of the same host will then usually differ in their crystal structures, depending on the respective guest. Since the combination of host and guest compound determines the lattice structure of the inclusion complex, the definition of host and guest may well be interchangeable. Such an inclusion complex will only be formed if its crystals are more stable than those of either the pure host or the pure guest compound.

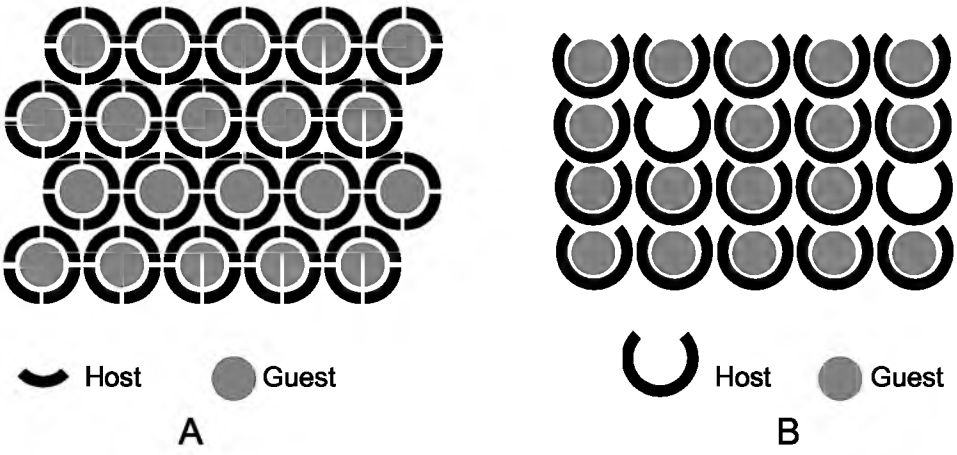



**Figure 1.1:** Polymolecular **A** and monomolecular **B** inclusion complexes

In general, host compounds are divided into two different classes, monomolecular and polymolecular. Cyclodextrines and crown-ethers are monomolecular hosts. They retain a central molecular void and form inclusion complexes whose host/guest ratios are not required to be stoichiometric. This is in contrast to polymolecular hosts, such as urea or deoxycholic acid, which themselves do not possess central voids. Their voids are created by the specific crystal lattices determined simultaneously by host and guest. In these compounds there will always be a stoichiometric ratio between host and guest. The Taddols, which are the forerunner as hosts in inclusion resolution experiments, are also representatives of this group. The following sections give an overview of the most important hosts that are known, ranging from inorganic to organic host compounds in order to illustrate their diversity. After an introduction of some selected inclusion complexes with inorganic guest compounds, inclusion complexes with organic host molecules will be described more extensively, finally focussing on chiral host compounds, which form the main subject of this thesis. A special paragraph deals with inclusion resolution, the selective inclusion of chiral guest compounds, leading to enantioseparation.

## 1.2 Inclusion complexes with inorganic and organometallic host substances[8]

A variety of inclusion complexes formed by inorganic or organometallic host compounds has been discovered throughout the years. The following paragraphs introduce the most common ones.

### 1.2.1 Metal-aromatic complexes[8]

A number of complexes of metals with aromatic compounds is known. These compounds with relatively strong metal-$\pi$ bond interactions can be considered as intermediate between ionic salts and inclusion complexes, which are controlled by hydrogen bonds or van der Waals interactions.

*Hofmann-type*

$Ni(CN)_2 \cdot NH_3 \cdot C_6H_6$, better known as Hofmann's benzene compound, is the first of the Hofmann-type and similar inclusion complexes created by a range of combinations between amine- or amine-metal (II)tetracyanometallate(II) hosts and aromatic guest compounds. In 1897, Hofmann's benzene compound was discovered by chance during the study of compounds obtained by the reaction of metal salts with hydrocarbons.

*Werner-type*

The general formula for Werner-type complexes is $MX_2A_4$, where M = $Fe^{2+}$, $Co^{2+}$, $Ni^{2+}$, $Cu^{2+}$, $Zn^{2+}$, $Cd^{2+}$, $Mn^{2+}$, $Hg^{2+}$, $Cr^{2+}$; X = $NCS^-$, $NCO^-$, $CN^-$, $NO_3^-$, $NO_2^-$, $Cl^-$, $Br^-$, $I^-$ and A = substituted pyridines, $\alpha$-aryl acyl amines, isoquinoline. Many Werner inclusion complexes with a wide variety of guests, ranging from noble gases to condensed aromatic hydrocarbons, are known in literature[8], and have been mainly investigated by Schäffler (he first applied "clathration" to mixture separation) and Radzitzky.

*Diisothiocyanatotetrakis ($\alpha$-arylalkylamine)Nickel(II) complexes*

Nickel thiocyanate, coordinated with four molecules of an $\alpha$-arylalkylamine, has the ability to selectively include a wide variety of aromatic compounds. An exchange of either the metal or the anion without loss of the inclusion ability is impossible. The host/guest ratio is dependant on both host and guest compound and, additionally, on the preparation method. In 1959, the research on more than 70 complexes was started by Hanotier and Radzitzky in order to expand the group of inclusion complexes of Schäffler.

### 1.2.2 Intercalation compounds[8]

An important and well-defined group of inclusion complexes are the intercalation compounds such as $H_3O^+/H_2O$ in $WO_3$. The guest compounds are reversibly inserted into a solid matrix that keeps its structural shape throughout intercalation or de-intercalation. The first host lattices described to go through intercalation reactions are graphite and aluminosilicates. Today, a large variety of host lattices with different structural dimensionality are known, most of them are transition metal/non-metal compounds. The lattice structure of the host and its properties allows certain guest compounds to be intercalated, such as atomic species (metal atoms, hydrogen) or a variety of molecular species of different size, geometry and composition.

### 1.2.3 Hydrates[8,20,22]

Hydrate inclusion complexes have a long scientific history, starting approximately 200 years ago. They are inclusion complexes of usually small molecules in water ice. Investigators in France and Germany discovered the majority of gas hydrates before 1900. Chlorine hydrate was first found by Davy in 1811, but its composition determined later by Faraday in 1823. The clathrates hydrates, also called gas hydrates, have been investigated most extensively, more so than the other two classes of hydrates. However, all three classes are of similar structural character, appearing from the water molecules which are the structurally dominant molecular species in these crystals. The ability to include a variety of compounds demonstrates a special property of the ice crystal.

### 1.2.4 Spirocyclophosphazenes[8]

Spirocyclophosphazenes have the general structure shown below.

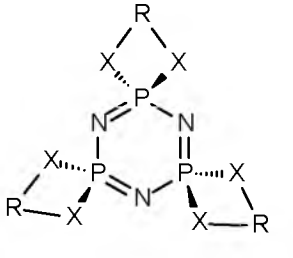



**Figure 1.2:** General structure of spirocyclophosphazenes

The group R is an aromatic organic group and X can be oxygen or nitrogen. The manner and speed of inclusion when pure spirocyclophosphazene comes into contact with organic liquids and vapours was unique at the time of discovery, as well as the use of the inclusion process in the separation of organic molecules of gross or subtle molecular size and shape differences. In addition, a modification of the channel or cavity size by variations in the type of organic spiro-side group attached to the phosphazene ring is possible. Examples of guest compounds range from aliphatic and aromatic hydrocarbons, olefins, halocarbons, esters,

ethers, ketones, nitriles, carbon disulfide to ethanol. The host/guest ratio differs with the molecular dimension of the guest (with molecules of large size being included in the highest ratio) and with the preparation method. Inclusion complexes prepared by crystallisation generally contain more of the guest. Removal of the guest results in crystal disruption.

### 1.2.5 Liquid clathrates[8]

The term "liquid clathrates" apparently contradicts itself, because clathrates are solid substances by definition. However, the transfer of the same basic concepts to liquids is possible. Liquid clathrates are nonstoichiometric liquid inclusion complexes, which show novel solution behaviour. Liquid clathrates belong to a class of liquid inclusion complexes formed by the interaction of aromatic guest compounds with host compounds related geometrically to $M[Al_2R_6X]$. The substances thus formed contain guest molecules in a certain ratio, but are not miscible with excess aromatic substances.

The hydrocarbon molecules in the liquid clathrates are locked in, similarly to inclusion in solid clathrates. They can be liberated by a change in temperature and then recovered. The first liquid clathrates, including aluminium alkyls, were prepared accidentally in 1969.

### 1.2.6 Zeolite[28]

Zeolites were discovered in 1756 by a Swedish mineralogist. Originally, they are natural minerals mined in many parts of the world. However, the majority of commercially used zeolites currently are synthetic. They are of major importance as catalysts and carriers in the petrochemical industry. Zeolites are a group of hydrated aluminosilicates of the alkali or alkaline earth metals (principally sodium, potassium, magnesium and calcium). They have three-dimensional crystalline structures containing (-Si-O-Al-). The silicon and aluminium atoms are tetrahedrally co-ordinated with each other through shared oxygen atoms. Each different framework topology has a unique system of channels and cavities characterising its honeycomb structure. The exchangeable cations often share the same channels and cavities as the guest molecules, and are normally located on more than one sub-lattice. Some structures are shown in Figure 1.3.

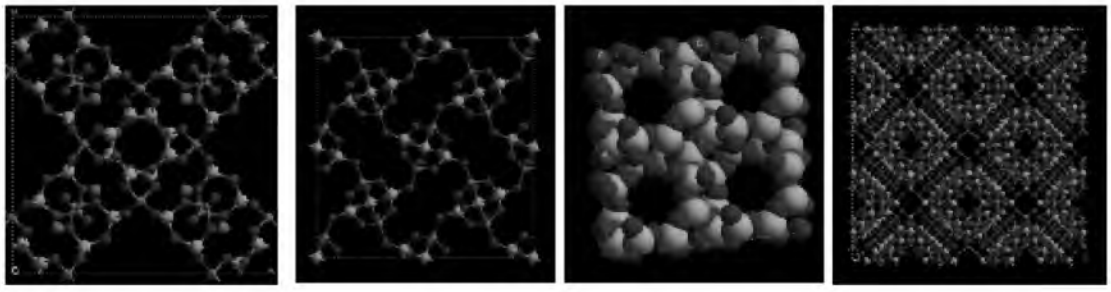


**Figure 1.3:** From left: Natrolite, Roggianite, Chabazite, Linde Type N

These (-Si-O-Al-) linkages create surface holes of fixed diameter and enclosed ordered channels and cavities, whose size depends on the chemical composition and the crystal structure of the respective zeolite. These cavities are able to shelter small molecules, such as cations or water.

The zeolitic channels have molecularly sized dimensions (molecular sieves). The size and shape of the channels effect the properties of these materials for absorption processes, which leads to their application in compound separation.

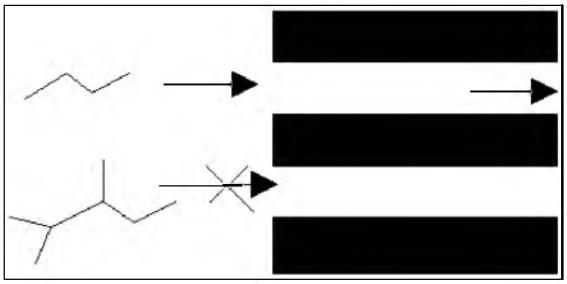


**Figure 1.4:** The sieve principle

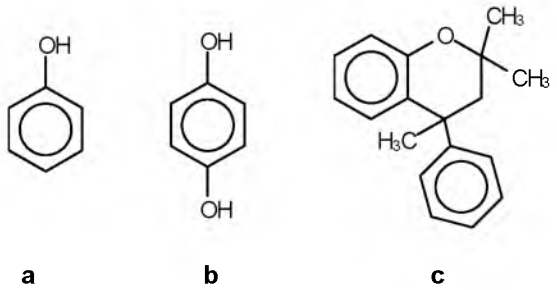
Zeolites absorb a variety of materials in large quantities, due to their high surface/volume ratio, without any change, chemically or physically in their structure.

## 1.3 Inclusion complexes formed by organic host compounds[8]

The following paragraphs deal with inclusion complexes formed by organic host molecules. Many organic hosts are already known, and new ones are continuously being developed. Only some of the most common examples are described below.

### 1.3.1 Phenoxy host compounds[8,24]

Host molecules possessing at least one aryloxy group are often found during the development of crystalline multimolecular inclusion complexes, such as phenol (a), hydroquinone (b) and Dianin's compound (c).




**a** **b** **c**

**Figure 1.5**: Key host molecules phenol (a), quinol (b) and Dianin's compound (c).

The inclusion capability of phenol was first observed in 1935 by Terres and Vollmer, who found the $H_2S$ adduct of phenol whilst examining the solubility of petroleum and tar components in liquid hydrogen sulfide. Nowadays a series of isomorphous clathrates with several guests, e.g. $H_2S$, $SO_2$, HBr, $CS_2$, noble gases, etc. and phenols as host component is known. The host system links, characteristically, the OH groups of six phenol molecules by hydrogen-bonding in such a way that the oxygen atoms form a hexagon from which the phenyl groups are pointing alternately above and below.

Wöhler found $H_2S$ to be included by quinol in 1849, Clemm found $SO_2$ to be similarly retained in 1859; and in 1886 Mylius observed the inclusion of CO. Mylius suggested the molecules to be "somehow able to lock" the volatile guest compounds without any chemical reaction. Finally, Powell firmly established the true cage or clathrates nature of these systems by X-ray studies in the 1940's. Quinol can exist in three crystal modifications, but only one is stable at room temperature. It can include small guest species, such as $CO_2$, $SO_2$ and noble gases.

Dianin's compound demonstrates the first approach to design new crystalline multimolecular host compounds.[8] It was first synthesised by the Russian chemist Dianin and is able to include various classes of guests such as argon, sulfur dioxide, iodine, ammonia, decalin, glycerol and sulfur fluoride.

### 1.3.2 Urea and urea derivatives[8]

In 1940, Bengen found, by accident, that urea has the ability to form a crystalline inclusion complex with octyl alcohol. Furthermore, he observed that a variety of linear organic compounds with at least six carbon atoms form such inclusion complexes with approximately six molecules of urea. Water or alcohols in a small amount were believed to catalyse the inclusion. These inclusion complexes decomposed into their constituents either by heating or by dissolving. Nowadays, an extremely diverse range of organic guests are known to be included in urea, such as alcohol and ether derivatives, aldehydes, ketones, carbocylic acids, dicarbocylic acids, amines, nitriles, mercaptanes and thioethers, provided that at least 6 carbon atoms are forming their main chains. The molecular ratio of urea and the number of carbon atoms of the guest compound to be included is not regular. The urea and thiourea lattices show selectivity, essentially controlled by the size of the available channels. Much effort has been put into the separation of components of a mixture on an industrial scale. Urea has been used to separate *n*-alkanes from branched or cyclic compounds whilst thiourea has been applied to separate benzene and cyclohexane from *n*-heptane.

The preparation of selenurea was firstly reported in 1884. It includes various hydrocarbons in its channels. Selenurea is, because of the smaller diameter of the channels, more selective in the choice of guests.

### 1.3.3 Perhydrotriphenylene[8]

Perhydrotriphenylene (PHTP) was firstly prepared in 1963 while investigating models of optically active polymers.

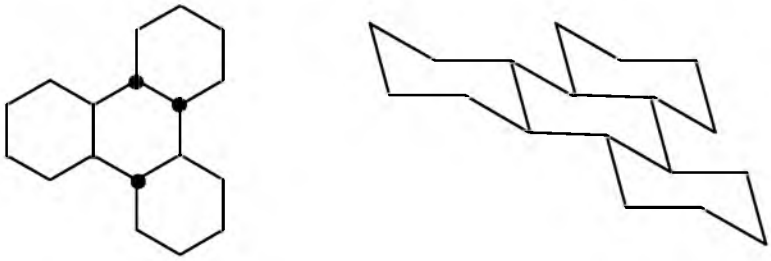


**Figure 1.6:** The most abundant isomer of PHTP, the *trans-anti-trans-anti-trans*-isomer

Its ability to form inclusion complexes was observed at the same time. Research was therefore performed in order to determine the physical and chemical properties as well as the structural requirements of an organic compound to be included as guest. A wide range of guests is mentioned, not only linear compounds (aliphatic hydrocarbons, mono- and dicarboxylic acids and their esters, linear alcohols, etc.), but also branched compounds (2,2,4, trimethylpentane), cyclic compounds (benzene, toluene, cyclohexane, dioxane, etc.) and in addition spherical or quasi-spherical molecules ($CCl_4$, etc.). The host/guest ratio inside the channels is just dependant on the total filling of the accessible space.

### 1.3.4 Cyclotriveratylene[8]

Cyclotriveratylene was first suggested by Robinson in 1915 to be 10,15-dihydro-2,3,7,8,12,13-hexamethoxy-5*H*-tribenzo[a,d,g]cyclononene (*n*=2). In the 1950's, a hexameric structure (*n*=6) was proposed on the basis of chemical studies and X-ray diffraction spectra by Italian chemists. Finally, Lindsey, Erdtman and Goldup performed investigations based on direct molecular weight determination and NMR-spectroscopy, and demonstrated in 1963-65 that Robinson's structure was in fact a trimer having $C_{3v}$ symmetry as shown in Figure 1.7.

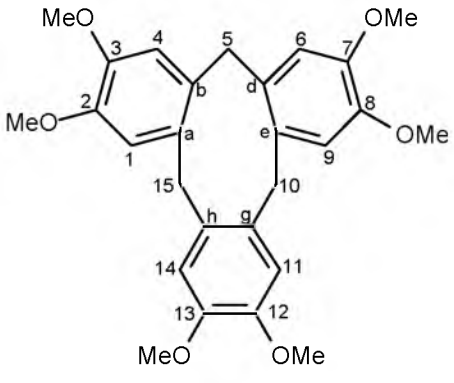



**Figure 1.7:** Cyclotriveratylene (CTV)

The ability of CTV to form stable inclusion complexes (crystalline solvates with water or benzene) was first observed by Bhagwat in 1931. Caglioti studied its inclusion behaviour in more detail in 1956. Starting with the observation that hexamethylated derivative cyclotricatechylene is more efficient in forming crystalline complexes than CTV. Several other analogs exhibiting inclusion capability have been described.
They form crystals, which are not packed very closely and can thus trap a variety of suitable guest compounds in their lattices.

### 1.3.5 Hexa-hosts[8]

The so-called hexa-hosts were synthesised as new hosts with controlled cavity geometry and should offer the possibility of studying the conformation, reactivity, and other properties of a given guest compound in a series of stereo-controlled environments.

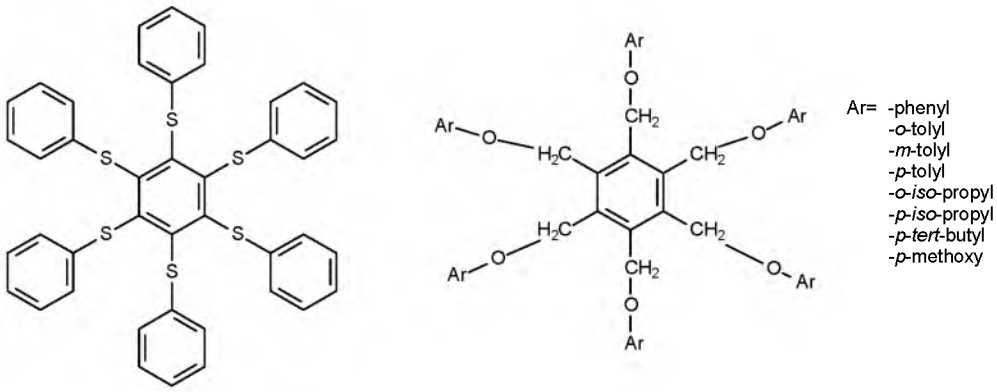



**Figure 1.8:** Examples of the first hexa-hosts studied

### 1.3.6 Tri-*o*-thymotide[8]

Tri-*o*-thymotide is known to form inclusion complexes of both channel and cavity types with a wide variety of chiral and achiral guest compounds.

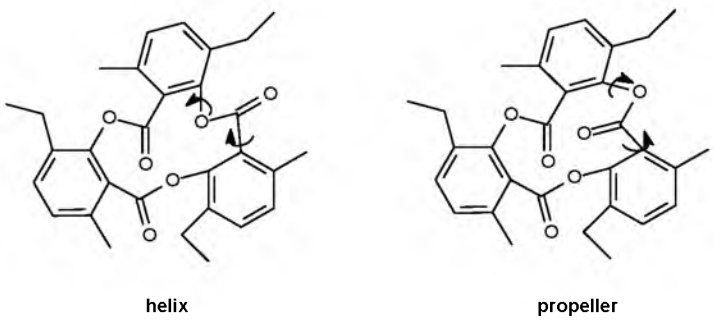
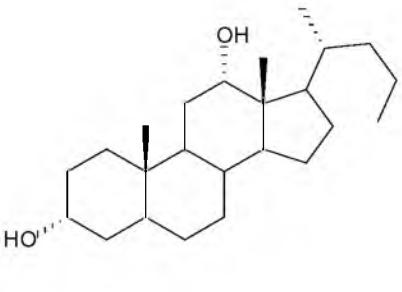



**Figure 1.9**: Tri-*o*-thymotide, a suitable host compound

Certain inclusion complexes undergo spontaneous resolution on crystallisation as a result of the solvated host molecules, adopting asymmetric propeller-like conformations of one chirality or the other. In solution, a mixture of enantiomeric propeller and enantiomeric helical structures are in equilibrium.

### 1.3.7 Deoxycholic acid[8,21,31]

DCA is a chiral bile acid, isolated from the biles of some animals.




DCA

**Figure 1.10:** Deoxycholic acid

A DCA molecule has two different sides, a polar and an apolar. The polar side is characterised by two secondary hydroxyl groups, whereas the apolar part contains two angular methyl groups. DCA behaves therefore in a hydrophilic as well as a hydrophobic manner. It forms stable channel inclusion complexes with a wide range of guest compounds, such as aromatic, aliphatic and alicyclic hydrocarbons, alcohols, ketones, fatty acids, esters, ethers, phenols, azo dyes, nitriles, peroxides and amines. The inclusion complexes formed between DCA and fatty acids have been thoroughly investigated.

## 1.4 Complex forming inclusion hosts[8,29]

Whereas the hosts described previously show strong complexation only in the solid phase, a large number of compounds that also form strong complexes with various compounds in solution will be described in the following section. It is often possible to crystallise these complexes.[17]

### 1.4.1 Crown ethers[8]

Macrocyclic polyethers have shown to possess efficient complexing properties towards metal cations, primary alkylammonium salts and other neutral and charged potential substrates.

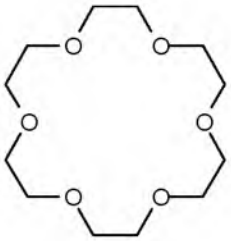


**Figure 1.11:** Unsubstituted 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6), the most intensively studied crown ether

With the aim to gain insight into the process of structured molecular complexation, methods for new design and synthesis of macrocyclic host molecules were developed. Petersen synthesised a series of macrocyclic polyethers with the name crown-ethers, so called because their three-dimensional shape resembles a crown. In crown-ether inclusion complexes, the usually smaller guest compound is bound to a cavity-like framework formed by the larger ether host in a structure reflecting a complementary stereoelectronic arrangement of the binding sites. Complexes of a crown-ether and a cation have both hydrophilic (outside) and hydrophobic (inside) parts.

### 1.4.2 Cryptate complexes[8]

The ion transport across biological membranes was explained in 1964 by Moore and Pressman by demonstrating the ionophore ("ion carrier") properties of valinomycin. The development of simple model systems to further study the mechanism of ion transport led to the development of various classes of molecules with cavities capable of binding other compounds.

Cryptates, which means "hidden", are macrobicyclic and macropolycyclic systems which completely hold the bound cation or anion in their cavities. The synthesis of the first macrobicycle was realised in 1968 by Lehn.

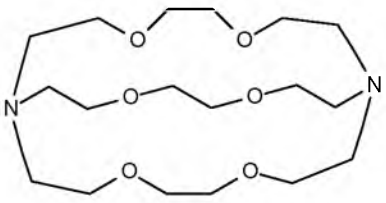


**Figure 1.12:** The first macrobicyclic polyether synthesised

### 1.4.3 Cyclodextrines[18,19,23]

Cyclodextrines (CD's) consist of a family of cyclic oligosaccharides obtained from starch by enzymatic degradation. They were first described by Villiers in 1891. Schardinger recognised the three naturally occurring CD's- $\alpha$, $\beta$ and $\gamma$, soon after the first observation. Until the 1930's, Pringsheim in Germany investigated the inclusion behaviour of CD's, demonstrating that they form stable hydrated complexes with many other chemicals. Structurally, CD's

consist of 6, 7, or 8 ($\alpha$, $\beta$, and $\gamma$ respectively) D-glucopyranosyl units connected by alpha-(1,4) glycosidic linkages. The most stable three dimensional molecular configuration has the shape of a toroid with the upper (larger) and lower (smaller) opening showing secondary and primary hydroxyl groups. As a result of the electron-rich environment provided by the glycosidic oxygen atoms, the inside of the toroid is hydrophobic.

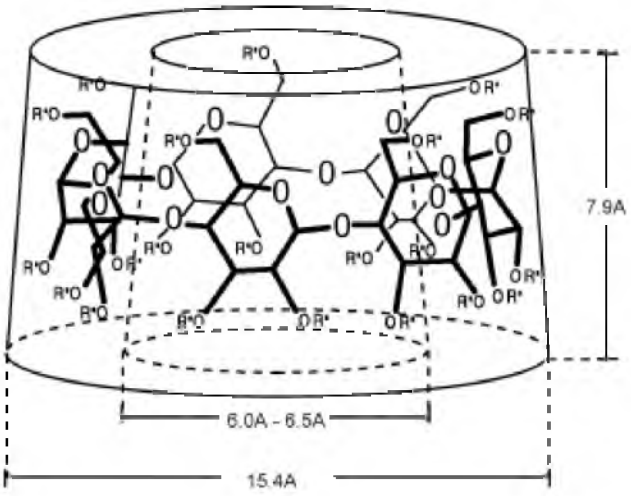



**Figure 1.13:** $\alpha$-cyclodextrine

Van der Waals forces, hydrogen bonding and solvent (hydrophobic) forces explain the stable complexes formed with compounds in the apolar environment of the CD's cavity. The complex depends on the concentrations of the CD, the guest and water.

The accommodation of the molecule in the cavity depends on the weak interactions taking place in the cavity, somewhat similar to those of enzymes. It was found that noble gases, paraffins, alcohols, carbocylic acids, aromatic dyes, benzene derivatives, salts, etc. are included, just to name a few of a long list of guest substances.

These characteristics of the CD's allow their use in drug delivery, because they enhance the drugs poor aqueous solubility, protect them in their micro-environment, create and maintain stable homogeneous distributions and can alter unpleasant physical properties (smell, taste).

## 1.5 Inclusion resolution

### 1.5.1 Introduction[26,27]

Inclusion resolution constitutes a new aspect in inclusion chemistry. Chiral host compounds are known and show in many cases chiral discrimination, allowing racemates to be resolved *via* inclusion complexation. This new application of inclusion complexes was explored by Toda in the 1980's. He synthesised a variety of new chiral host compounds and tested them for their inclusion capabilities on uncharged, racemic guest compounds. The separation of compound mixtures *via* inclusion crystallisation was already known and applied, but a

resolution *via* inclusion complexation was relatively new and unexplored at that time. It is based on chiral discrimination and recognition in the crystalline phase. The principle is simple: if a chiral host recognises the chirality of the guest compound and includes only one enantiomer selectively, it can be used for the optical resolution of this guest compound.
It is also possible to perform reactions in the solid state in inclusion complexes. In the case of prochiral compounds in a chiral lattice formed by enantiopure hosts, this may lead to enantioselective reactions.
Before giving an overview of developments in inclusion resolution, a short introduction of chirality and its consequences is given.

### 1.5.2 Chirality[10,11]

All objects have mirror images. According to their symmetry, they can be divided into three categories, achiral (a), dissymmetric chiral (b) and asymmetric chiral (c) (Figure 1.14).

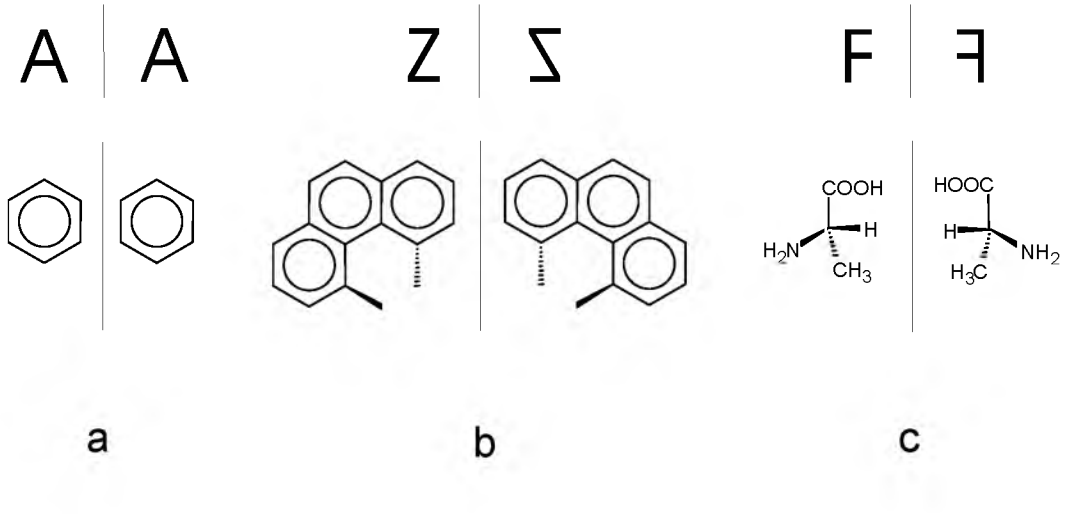



**Figure 1.14:** Two-dimensional and three-dimensional examples for mirror images;
**a** achiral, **b** dissymmetric chiral, **c** asymmetric chiral

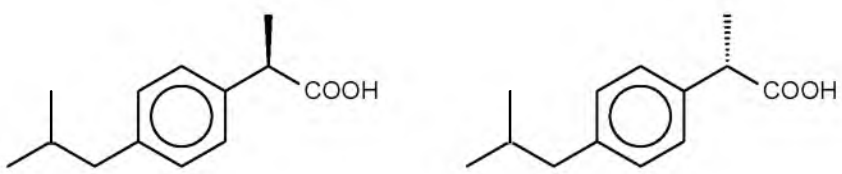
Objects that do not possess rotation-reflection axes of symmetry ($S_n$) are called chiral (CIP, 1966). The term "chiral" derives from the Greek word for hand ("cheir"). The letters **Z** and **F** (Figure 1.14) are both chiral objects, but differ in symmetry. **Z** possesses a twofold rotation axis ($C_2$), whereas **F** is not symmetric at all. In general, all objects containing rotation axes ($C_n$) are called dissymmetric chiral, and objects without any symmetry are called asymmetric chiral. The mirror images of chiral items are non-superposable. The opposite of chiral is achiral. All objects superposable on their mirror images are called achiral, e.g. the letter **A**.

### 1.5.3 Consequences of chirality[12,13,30,37]

Chirality constitutes a fundamental property of the building blocks of life, such as amino acids and sugars. Biological systems, which mediate metabolic and regulatory processes, are therefore sensitive to stereochemistry. As a consequence, stereochemistry has to be taken into consideration when studying xenobiotics, such as food additives, drugs, flavours, fragrances and agrochemicals.

Enormous effort is therefore spent on the development of enantiopure compounds, drugs especially. Their application is strictly regulated in Europe and the USA. The American Food and Drug Administration (FDA) in particular puts force into the development of chiral drugs by aggravating the process of patenting new racemic drugs. Furthermore, a new market policy has been developed, "The racemic switch". An enantiopure drug, whose racemic form is already patented, is developed and newly patented in order to extend a company's patent protection for efficacious and profitable drugs.

In contrast to the drugs coming from natural sources, which mainly are obtained enantiopure, most synthetic drugs are racemates. Although often just one enantiomer is of therapeutical value, some drugs are applied in racemic forms. An example is shown below.



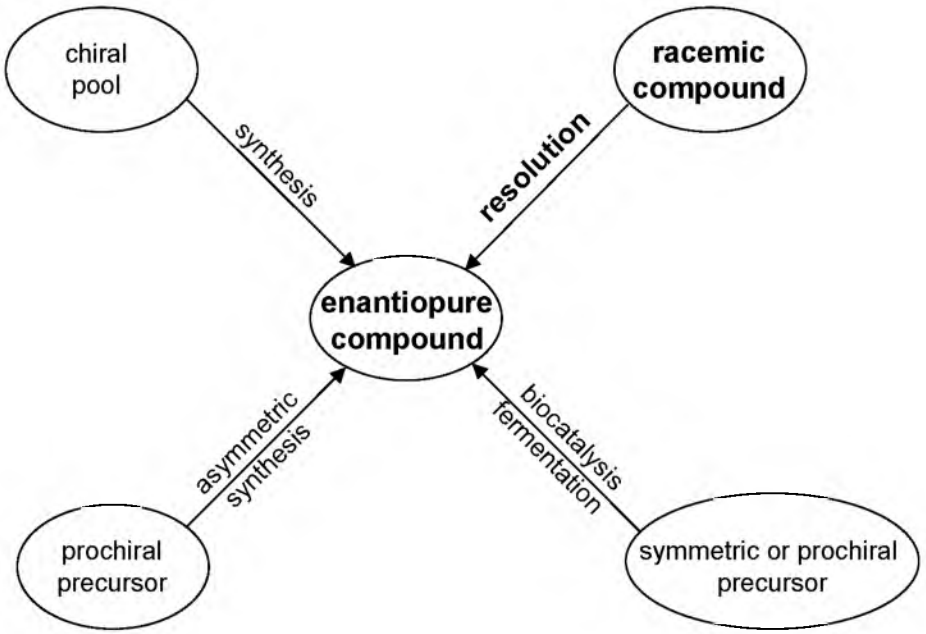

**(*R*)-ibuprofen**
inactive

**(*S*)-ibuprofen**
anti-inflammatory, analgestic

**Figure 1.15:** The two enantiomers of ibuprofen and their medicinal effect

Nowadays, the production and thus application of racemic drugs is decreasing as more enantiopure compounds conquer the market, encouraged by factors like efficacy, regulation and economic factors. The requirement for enantiopure compounds or enantiopure starting material for their syntheses is therefore high.

Scheme 1.1 (following page) shows the general methods used to obtain enantiopure compounds.



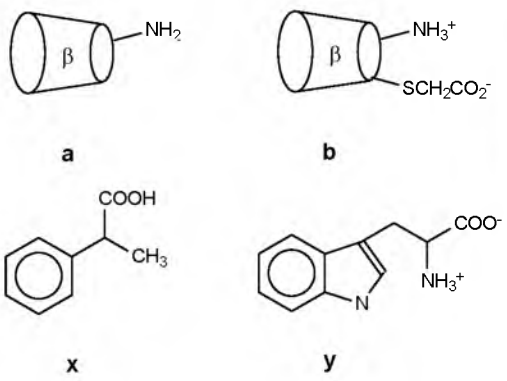

**Scheme 1.1:** General routes to enantiopure compounds

The method applied is dependent on several factors: in large scale production the chiral pool or fermentation is mostly applied, whereas in fine chemistry the use of resolution methods is predominant, with biocatalysis rapidly gaining in importance. Inclusion resolution especially constitutes a relatively new way of isolating enantiomers. It offers potential advantages compared to the already established processes, such as better prospect for *in situ* racemisation (asymmetric transformation) or dynamic resolution and not being limited to ionisable compounds. However, up to now, inclusion resolution has rarely been studied and little is known about the scope and limitations, in particular with respect to application in industry.

A number of literature examples is presented below. The most relevant examples, the Taddols, will be discussed in more detail in chapter 2.

### 1.5.4 Modified cyclodextrins[35]

Cyclodextrins can easily form diastereomeric complexes with a racemic guest compound due to the highly chiral cavity present in these molecules. The chiral discrimination of unmodified cyclodextrins and their application in chromatography has been intensively studied by Armstrong. The difference between the stability of the diastereomeric complexes is highly dependent on the nature of the cyclodextrin, therefore, modified cyclodextrins have been investigated in inclusion resolution by Easton and Lincoln[1].



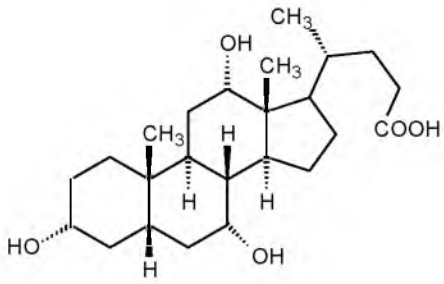

| cyclodexdrin | guest | $K_R$ ($dm^3mol^{-1}$) | $K_S$ ($dm^3mol^{-1}$) | $K_R/K_S$ |
|---|---|---|---|---|
| a | x-$H^+$ | 36 | 13 | 2.8 |
| b | y | 15 | 11 | 1.4 |

K = association constant

**Figure 1.16:** Inclusion behaviour of modified cyclodextrins

### 1.5.5 Cholic acid[15]

Bile acids and their derivatives have recently shown to be useful host compounds in inclusion resolution. Cholic acid, for example, is able to resolve a number of epoxides by adsorption[2].




3α,7α,12α-trihydroxy-5β-cholan-24-oic acid

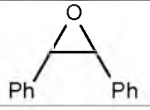
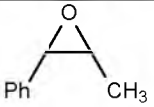
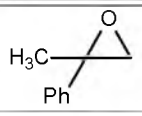
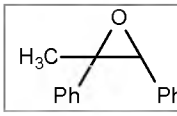
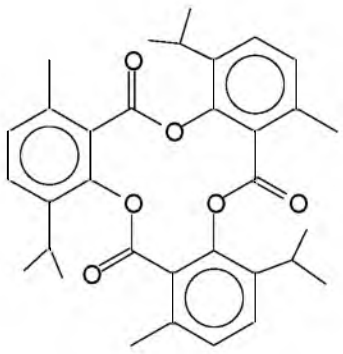
| racemate | e.e.% | config. | host:guest |
|---|---|---|---|
|  | 95 | (-)-*S,S* | 2:1 |
|  | 64 | (-)-*S,S* | 2:1 |
|  | 16 | (+)-*R* | 2:1 |
|  | 67 | (+)-*R,R* | 5:2 |

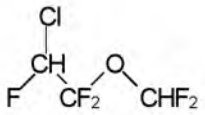
**Figure 1.17:** Optical resolution of epoxides *via* inclusion complexation with cholic acid

### 1.5.6 Tri-o-thymotide

Tri-o-thymotide (TOT) is able to resolve enflurane, a common anesthetic, by formation of a cage-type inclusion complex[3].



TOT



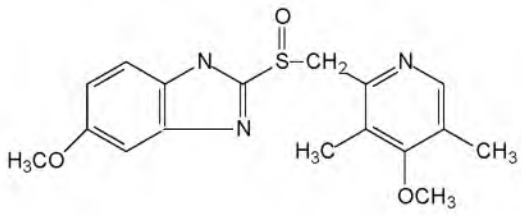
Enflurane

**Figure 1.18**: Tri-o-thymotide and rac. enflurane

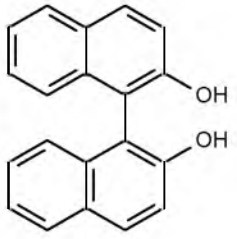
TOT is an interconverting racemic mixture of stereogenic structures in solution, but while crystallising with suitable guest substances, well-defined chiral chlathrate complexes are formed. It is able to include enflurane, affording an *e.e.* of 38%.

### 1.5.7 Binol[32]

2,2'-dihydroxy-1,1'-binaphtyl (Binol), a well known component of many enantioselective catalytic systems, is able to resolve omeprazole, a highly potent gastric acid secretion inhibitor (firstly on the market as racemate, Astra Zeneca, 1988) affording an *e.e.*>99% in a host/guest ratio of 1:1[4].



omeprazole



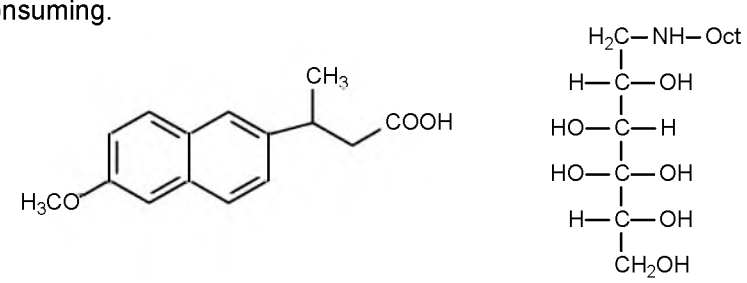
binol

**Figure 1.19:** Omeprazole can be resolved *via* inclusion complexation with host Binol

Omeprazole is an example of the so-called "racemic switch". It was first approved and patented as a racemate, but with the development of the enantiopure drug ((*S*)-omeprazole), a new patent was obtained. Market introduction under the trade name Nexium® has just started.

### 1.5.8 N-octyl-glucamine

N-octyl-glucamine is able to resolve naproxen affording the (+)-enantiomer with an *e.e.* of >95%. Naproxen (6-methoxy-α-methyl-2-naphthaleneacetic acid) is a popular non-steriodal, anti-inflammatory and analgesic drug.[5] The (+)-enantiomer is about 28 times more effective than the (-)-enantiomer. The asymmetric synthesis of (+)-naproxen is possible, but costly and time-consuming.




**naproxen** **_N_-octyl-_D_-(-)-glucamine**

**Figure 1.20:** Naproxen and its host *N*-octyl-glucamine

### 1.5.9 Lactic acid derivatives and diol hosts[16,33,38-81]

Weber investigated diphenylcarbinol derivatives of lactic acid as potential host compounds and found them to be suitable compounds for the resolution of some chiral alcohols. Figure 1.21 shows the dimeric host complex with (*R*)-3-methylcyclohexanone. The application of such a simple, easily obtainable host compounds is attractive from an industrial point of view. A co-current Ph.D thesis by M.C. Afraz[82] on resolution covers this type of compounds.

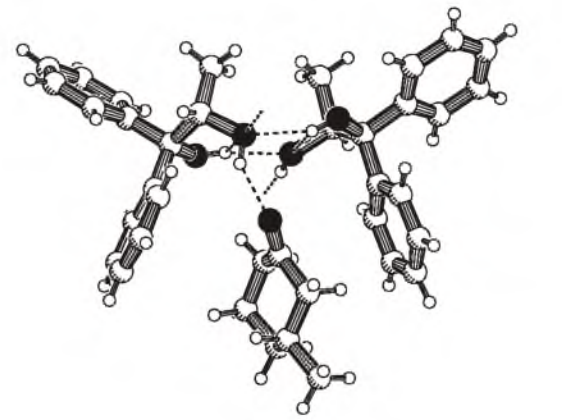


**Figure 1.21:** (*R*)-3-methylcyclohexanone accommodated in the dimeric diphenylcarbinol derivative of lactic acid

Industrial attention is also attracted by several other diol host compounds. Many, mostly small chiral molecules can be separated by inclusion crystallisation with various diol host compounds often with high *e.e.*'s and in good yield (for detail see chapter 2, appendix). The most effective and intensively investigated hosts developed and studied by Toda are shown in Figure 1.22.

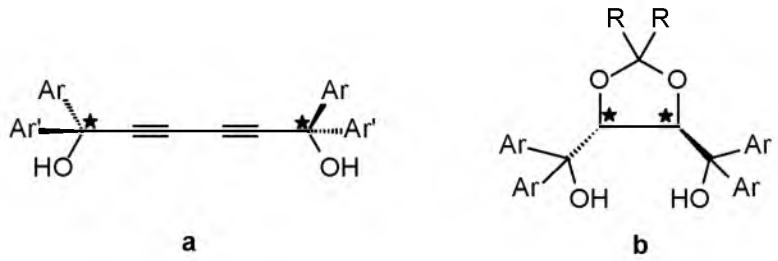
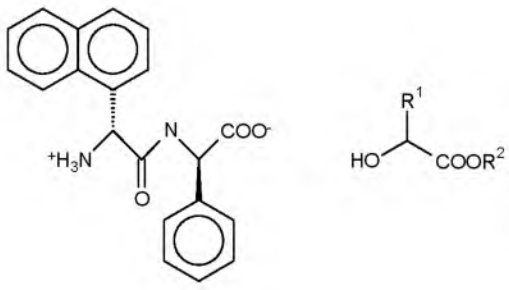



**Figure 1.22:** Diol hosts used by Toda, **a**: acetylenic alcohols, **b**: Taddols

### 1.5.10 Dipeptides[14,34]

A recent development is the use of simple dipeptides and their derivatives as chiral host compounds. For example, (*R*)-(1-naphtyl)glycyl-(*R*)-phenylglycine **a** is able to resolve several $\alpha$-hydroxy esters **b** with high enantioselectivity.[6]




| $R^1$ | $R^2$ | host:guest | *e.e.*% | config. |
|---|---|---|---|---|
| Me | Me | 1:1 | 89 | *S* |
| Me | Et | 1:1 | 97 | *S* |
| Et | Me | 1:1 | 87 | *S* |
| *n*-Pr | Me | 1:2 | 89 | *S* |
| *n*-Bu | Me | 1:2 | 99 | *S* |
| *i*-Bu | Me | 1:2 | 87 | *S* |

**Figure 1.23:** Inclusion resolution of esters with dipeptide host **a** found by Akazome

The dipeptide forms a chiral pocket-like cavity for inclusion of guest compounds, constructed from the naphthyl groups. A more detailed description of these compounds is given in chapter 5.

### 1.5.11 Inclusion resolution combined with asymmetric transformation

All classical resolution methods have one disadvantage in common; the maximum yield of the desired enantiomer from the racemate is limited to 50%, leaving the undesired enantiomer as an economical and environmental problem. A technique of resolution

combined with racemisation, the so-called asymmetric transformation, could alleviate this problem.

Inclusion resolution offers good possibilities for the application of asymmetric transformation, as shown by Kaku.[7] The Taddol-like compound **a** preferably includes the *(R)*-enantiomers of several substituted cycloalkanes. Base catalysed racemisation of **b** leads to a thermodynamically controlled de-racemisation of the ketones in presence of Taddol **a**. An increase of yield and *e.e.* compared to the normal inclusion resolution, without simultaneous racemisation, has thus been achieved.

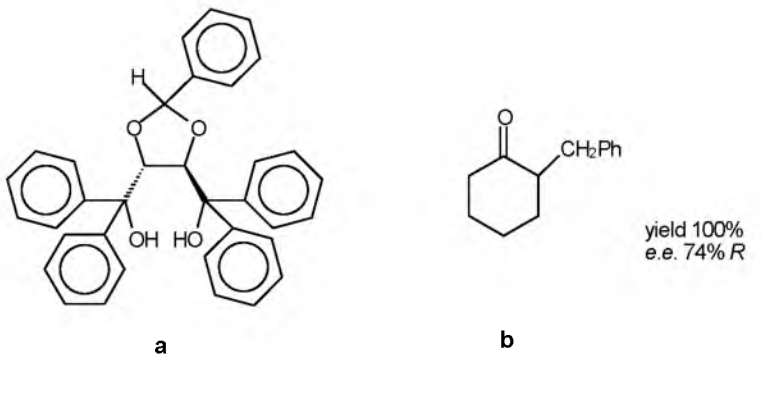



**Figure 1.24:** Successfully combined inclusion resolution and asymmetric transformation

## 1.6 Objective and outline of the thesis

The research described in this thesis is focussed on the further development of inclusion resolution, which needs a more thorough understanding to allow industrial application. Little is known at this moment about the scope and limitations of this technique for obtaining enantiopure compounds. Taddols and dipeptides, which have proven to be suitable host compounds, were taken as lead compounds in this study of inclusion resolution. The objective here is not just the development of new inclusion hosts and their application in resolutions, but mainly the search for a suitable system to fundamentally investigate the physico-chemical basis of such an inclusion resolution process. Knowledge about the behaviour of mixtures of diastereomeric inclusion complexes in relation to their different compositions is required to understand the thermodynamics of the inclusion resolution process. The determination of phase diagrams constitutes the first step in obtaining a more detailed knowledge about that process. It is a well-known fact that in classical resolution the diastereomeric salts crystallise separately and in most cases do show solid solution behaviour[35] in which both enantiomers are present in the same crystal. The success of the method of resolution *via* diastereomeric salts depends for a large part on this behaviour, as do the practical rules and approaches.

In inclusion resolution, much weaker interactions are controlling the process and it is therefore of great importance to establish in how far the practical experience, which has been obtained in classical resolution since its discovery, can be transferred to inclusion resolution. This thesis aims to be a first step in this direction.

**Chapter 2** deals with the synthesis of some Taddols, a class of capable and promising host compounds based on optically pure tartaric acid. It points out the importance of the Taddols in inclusion resolution by giving an overview of successful experiments performed by Toda.

In **Chapter 3**, the inclusion capabilities of newly designed and already known Taddols were tested. A wide variety of racemic compounds such as alcohols, organic acids, amines, nitriles and ketones have been used. The Taddols have been applied individually as well as in mixtures in several inclusion resolution experiments using various techniques.

**Chapter 4** describes the physico-chemical aspects of selected inclusion resolution experiments with Taddols as host compounds. For the first time, binary phase diagrams and a ternary phase diagram of inclusion complexes have been recorded.

In **Chapter 5**, the inclusion capabilities of dipeptide host compounds *via* sorption and crystallisation are described. A diversity of racemic compounds such as alcohols, sulfoxides and ketones have been used.

Summaries conclude this thesis.

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# 2 Taddols, a successful example in inclusion resolution

*This chapter deals with the synthesis of some new and known Taddols, a class of capable and promising host compounds based on optically pure tartaric acid. It shows the importance of the Taddols in inclusion resolution by giving an overview of successful experiments performed by Toda.*

## 2.1 Introduction

As discussed in chapter 1, inclusion resolution has a number of potential advantages compared to classical resolution *via* diastereomeric salt formation. The most important one is not being restricted to acids and bases, therefore the problem of inorganic waste salts formed during recovery does not occur. The isolation of the pure enantiomer and recovery of the pure host compound can, in principle, be accomplished waste-free. Contrary to classical resolution, the straightforward development of asymmetric transformations is expected to be less problematic. The use of strong acids or bases in asymmetric transformations to racemise the undesired, not included enantiomer *in situ*, has less influence on the resolution, whereas the presence of strong acids or bases in a classical resolution process impairs the salt formation and thus the quality of the resolution. Hence, inclusion resolution offers the potential of 100% yield and 100% *e.e.*.

The first successful examples of inclusion resolution using Taddol-derived host compounds were developed at the end of the 80's. Since then only a limited number of other hosts have been developed and applied successfully in inclusion resolution. For that reason it is worth to use the Taddol's for a thorough study of the fundamental aspects, scope and limitations of inclusion resolution.

## 2.2 Taddols- the hosts of choice

### 2.2.1 Introduction

A thorough study of all aspects of inclusion resolution requires suitable and stable host molecules. Their ability to include a variety of guest molecules should have been already proven and an expansion to develop new resolutions with these hosts should still be possible. Furthermore, the host compound or its precursor should be readily accessible with respect to disposability as well as synthesis.

In particular *Prof. Fumio Toda* and his co-workers have evolved several highly successful classes of compounds for use in inclusion resolution. With these agents, a substantial number of procedures to separate enantiomers in high enantiomeric excess and good yield have been developed. Compounds based on tartaric acid with the general structure depicted in Figure 2.1 have been studied most extensively by *Toda*[1,2,3,4,5,6,7,8,9,10,11,15] and some other authors[12,13,14,19]. This class of compounds, the so-called Taddol's, has been established as useful auxiliaries not only in inclusion resolution, but also in asymmetric synthesis[52-54]. They have also been discovered as remarkable auxiliaries in the application of several techniques towards the synthesis of enantiopure compounds[55-59]. Metal complexes have been developed[47,51] and used for nucleophilic addition to aldehydes in reactions of stoichiometric or catalytic character. The range of their application follows further from the use in the asymmetric reductions of ketones,

in tandem cycloadditions and ene-reactions, to playing important roles in the induction of enantioselectivity in the cyanohydrin-addition. Furthermore, derivatives of the Taddols are known which can be polymerised and grafted with the aim of incorporating them into immobilised solid-phase catalysts. Supramolecular chemists are interested in Taddols because of their efficiency as doping agents for phase transformations from nematic into cholesteric liquid crystals. However, our main interest in Taddols is based on their ability to form clathrates with a variety of organic compounds, which are useful for the resolution of racemates as well as in enantioselective solid phase reactions.

Based on the versatility of these Taddols in inclusion resolution and their simple preparation from readily available optically pure materials, they were selected as model compounds for the study described in this thesis.

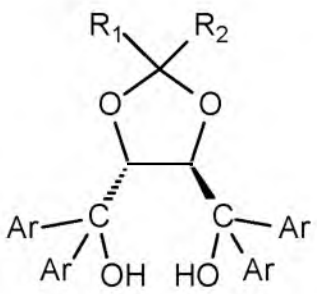



**Figure 2.1:** General structure of possible hosts (Taddols) for inclusion complexation

The Taddol derivatives have a fairly rigid structure, containing two adjacent diarylcarbinol groups *trans* to each other at the extremities of a 1,3-dioxolane ring. They have polar functionalities which control the accommodation of guest molecules in their cavities caused by hydrogen bonding. Crystal structure analyses of several Taddols and Taddol inclusion complexes revealed the close proximity of the hydroxy groups towards each other by hydrogen bonding, which prevents a free rotation of the diarylcarbinol groups and is responsible for the rigid structure.

The Taddols are based on enantiopure tartaric acid, whose two enantiomers are available in large quantities. Their syntheses are uncomplicated and fast, sometimes requiring the development of suitable purification techniques (see section 2.3).

Wide variations in the aromatic, as well as the aliphatic, part of the molecule offer the opportunity to synthesise new Taddol-like compounds and to create a variety of similarly structured compounds suitable for the study of the scope and limitations and hopefully also for the use in Dutch Resolution[62] experiments, in which structurally related families of resolving agents are required (see section 3.4).

### 2.2.2 Taddols in inclusion complexation

Chiral Taddols favour the crystallisation together with small organic compounds in one crystal lattice.[29] They constitute therefore perfect candidates for the separation of enantiomers *via* inclusion complexation. Moreover, diastereomers and other geometric isomers can also be separated in this way.

Inclusion crystals of Taddols with a potential guest can be obtained using several techniques, ranging from solutions to solvent free methods. Figure 2.2 gives an overview of these methods.

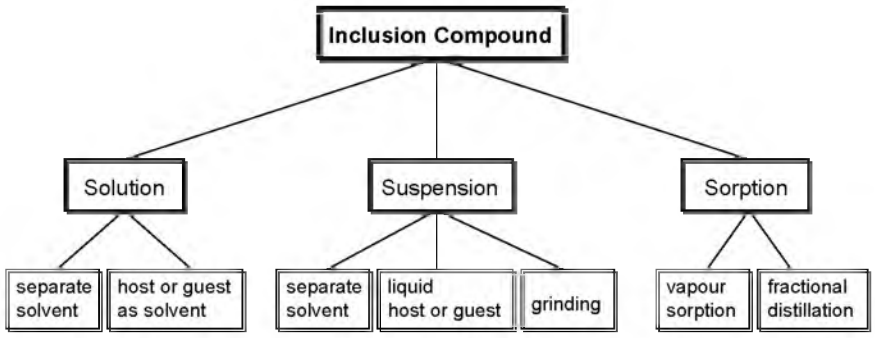



**Figure 2.2:** Different methods to obtain inclusion crystals

The most common and known technique is still the crystallisation from solution using a separate solvent. Inclusion crystals can also be obtained from solution without an additional solvent, simply by dissolving the host compound in the pure, liquid guest compound or *vice versa*.

Three different techniques are combined in the second method, the suspension approach. Liquid sorption is an almost solvent-free method. Both host and guest are stirred as a suspension in a solvent such as hexane or water, in which they have a low solubility. By slowly dissolving and crystallising, stable inclusion crystals can be formed, whose solubility is even lower compared to the solubilities of both compounds separately. Analogously, this method can be applied without a separate solvent. Thirdly, the method of grinding can be used. Both host and guest are mixed and ground in a mortar until inclusion crystals are formed. This method can also be seen as a sorption technique.

Vapour sorption constitutes another solvent-free method. The guest compound is heated and led gaseously over the solid host compound. Inclusion occurs by sorption of guest molecules into the host molecules. An elegant method comprises distillation of a host/guest mixture in which the non-complexed enantiomer of the guest distils first, followed by the complexed enantiomer at the decomposition temperature of the inclusion complex. The latter method constitutes a combination of the formation and separation of inclusion crystals. Host and guest can be separated by many methods; the two most commonly applied techniques are distillation and selective crystallisation. Distillation of the guest from the host requires firstly a large

difference in the boiling points of both, host and guest. Secondly the stability of the inclusion complex should be low enough, as is usually the case.
Selective crystallisation involves the addition of a second guest molecule, which is able to form a stronger complex with the respective host. The more stable host/guest complex will precipitate and after filtration and evaporating the solvent, the pure separated guest compound will be obtained in high purity and a high yield as well.

Developing an inclusion resolution is, like classical resolution, more or less a process of "trial and error", depending largely on serendipity. However, an analysis of the compounds resolved by Toda (see appendix) clearly shows a remarkable difference to classical resolution. In classical resolution, small structural changes of the compound to be resolved lead to large differences in the result of resolution, i.e. very often the requirement of a different resolving agent. In contrast, the combined results of Toda's work reflect that series of structurally related compounds can often be included and resolved by the same, or a similar host compound. The weaker interactions in inclusion complexes apparently allow a greater flexibility compared to the strong electrostatic interactions in diastereomeric salts.
Toda's remarkable success in the field of inclusion resolution can be partial explained as follows: taking families of structurally related compounds as single entities, the number of different compounds included is more limited as is apparent at first sight. In this way, the number of successful examples can be reduced from 87 to 30, leaving additional scope for new examples and research.
Although the application of inclusion resolution is indeed promising, still the requirement of prediction is left to be solved. On the resolution of a given racemate, the whole range of Taddol-like compounds can be tested, but no prediction can be made about the efficiency or even the occurrence of a separation. Obtaining any resolution is simply a matter of coincidence. A good example is depicted in Figure 2.3.[15]

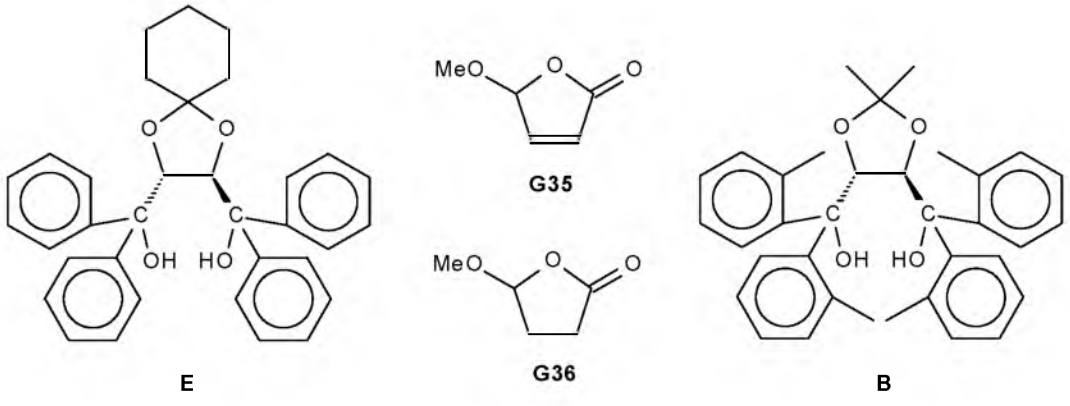



**Figure 2.3:** Example of Taddol inclusion complexes

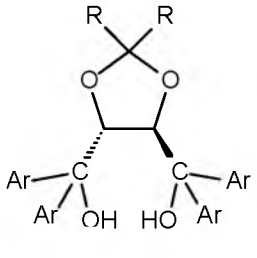
Taddol **E** is able to resolve racemate **G35** by formation of an inclusion complex with the (+)-butenolide **G35** affording an *e.e.* of 18% and a yield of 91% (see appendix, entry 52). A similar

compound, the saturated lactone **G36** is not included or resolved by the same host, although an inclusion would be expected, since **G35** and **G36** are structurally related.

Taddol **B** is also able to resolve **G35**, resulting in inclusion of the (+)-butenolide **G35** with a high *e.e.* of 92%, but a lower yield of 41% (see appendix, entry 54). In addition, **B** is able to resolve **G36** as well, but preferably the (-)-isomer is included with an *e.e.* of 96% and a yield of 50% (see appendix, entry 56). Both, the maximum *e.e.* and yield obtainable are 100 % in all of Toda's experiments.

Furthermore, it should be noted, that in all three cases of inclusion resolution, the crystals were obtained by the method of crystallisation from solution. The application of the liquid sorption technique did not lead to inclusion crystals in these cases (see appendix, entries 53,55,57). As this example has proven, the method applied also highly influences the process of developing a new inclusion resolution.

Besides this example described above (Figure 2.3), Toda and his co-workers have developed a variety of inclusion resolutions using five different Taddols as host compounds (Figure 2.4).




R = -$CH_3$
Ar = -phenyl **A**
-*o*-tolyl **B**
-*p*-tolyl **C**

R = -$(CH_2)_4$
Ar = -phenyl **D**

R = -$(CH_2)_5$
Ar = -phenyl **E**

**Figure 2.4:** Five Taddols used by Toda and co-workers

The appendix of this chapter gives an overview of the diversity of compounds split by the Toda-group: amines, *N*-heterocycles, alcohols, phenols, ethers, ketones, esters, lactones, anhydrides, sulfoxides, amino acid esters, hydroxy acid esters, cyanohydrins, alkoxylactones, and oxaziridines. The inclusion crystals display host/guest ratios in diverse orders: the most common ratio is 1:1. In general, Toda reached the most efficient resolutions using the sorption technique. A comparison of the efficiencies of sorption, crystallisation and distillation is collected in the following table.

| | sorption | | crystallisation | | distillation | |
|---|---|---|---|---|---|---|
| efficiency S | number of experiments | % | number of experiments | % | number of experiments | % |
| 0.9-1.0 | 1 | 2 | 0 | 0 | 1 | 5 |
| 0.6-0.8 | 25 | 41 | 5 | 11 | 4 | 21 |
| 0.3-0.5 | 13 | 21 | 30 | 64 | 10 | 53 |
| 0.0-0.2 | 22 | 36 | 12 | 26 | 4 | 21 |
| total | 61 | | 47 | | 19 | |

for details see appendix

**Table 2.1:** Comparison of efficiencies of resolutions performed by Toda

Toda never reached an efficiency higher than 0.8 in all resolutions performed by the crystallisation method, whereas 2% of all attempts using the method of sorption and 5% of the distillation method led to very high efficiencies (both as single examples only).
A comparison of the efficiencies of the compounds resolved in the *Toda*-group is given in Table 2.2.

| compound | number | $S_{average}$ | $S_{min}$ | $S_{max}$ |
|---|---|---|---|---|
| cycles | 113 | 0.44 | 0 | 1 |
| bicycles | 63 | 0.41 | 0 | 0.8 |
| ketones | 54 | 0.48 | 0.1 | 0.8 |
| amines | 40 | 0.38 | 0 | 1 |
| alcohols | 38 | 0.45 | 0.1 | 0.8 |
| aromatics | 38 | 0.43 | 0 | 1 |
| esters | 19 | 0.45 | 0 | 0.9 |
| sulfoxides | 4 | 0.50 | 0.2 | 0.8 |

for details see appendix

**Table 2.2:** Comparison of efficiencies of resolutions of different compound classes performed by Toda

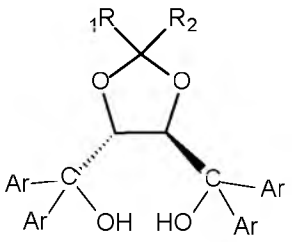
The highest average efficiency has been obtained for sulfoxides, closely followed by ketones. Amines exhibit the lowest resolution efficiency in all experiments performed by Toda and co-workers. However, single examples for each compound class have high efficiencies.

In summary, the Taddols offer a high potential for the use in inclusion resolution, dealing with many racemates and a variety of experimental techniques. The average quality of this type of resolution is rather moderate. However, a way to predict and finally design new resolutions cannot yet be seen from his results.

## 2.3 Synthesis of potential Taddol-like host compounds

### 2.3.1 Introduction

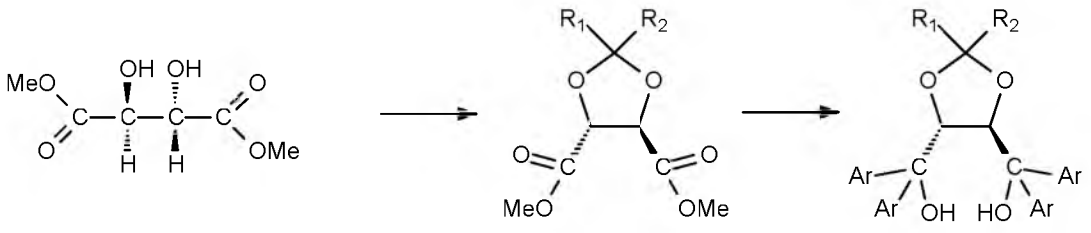
The following twelve Taddols were synthesised in order to investigate their inclusion capabilities and to gain insight into the scope and limitations of Taddols with respect to resolution. Several of them were already known and have been described in literature[1-48]. To further expand the scope of this study, the new Taddols **3**, **6** and **10 – 12** were also prepared.



| | | | |
|---|---|---|---|
| $R_1,R_2$ = -methyl | | $R_1,R_2$ = -cyclohexyl | |
| Ar = -phenyl | **1** | Ar = -phenyl | **9** |
| -*o*-tolyl | **2** | -*p*-tolyl | **10** |
| -*m*-tolyl | **3** | | |
| -*p*-tolyl | **4** | | |
| -*o*-anisyl | **5** | | |
| -*m*-anisyl | **6** | Ar = -*p*-tolyl | |
| -*p*-anisyl | **7** | $R_1,R_2$ = -H | **11** |
| -*p*-Cl-phenyl | **8** | $R_1$ = -H, $R_2$ = -phenyl | **12** |

**Figure 2.5:** Taddols synthesised

The already known host compounds, as well as the five new Taddols will be used to extend the search for separations of new racemates *via* inclusion complexation. Furthermore, it addresses the question whether inclusion resolutions are restricted to the application of a single Taddol-type compound and whether the use of mixtures of Taddols constitutes an improvement.
The syntheses of the Taddols require two reaction steps (Scheme 2.1).



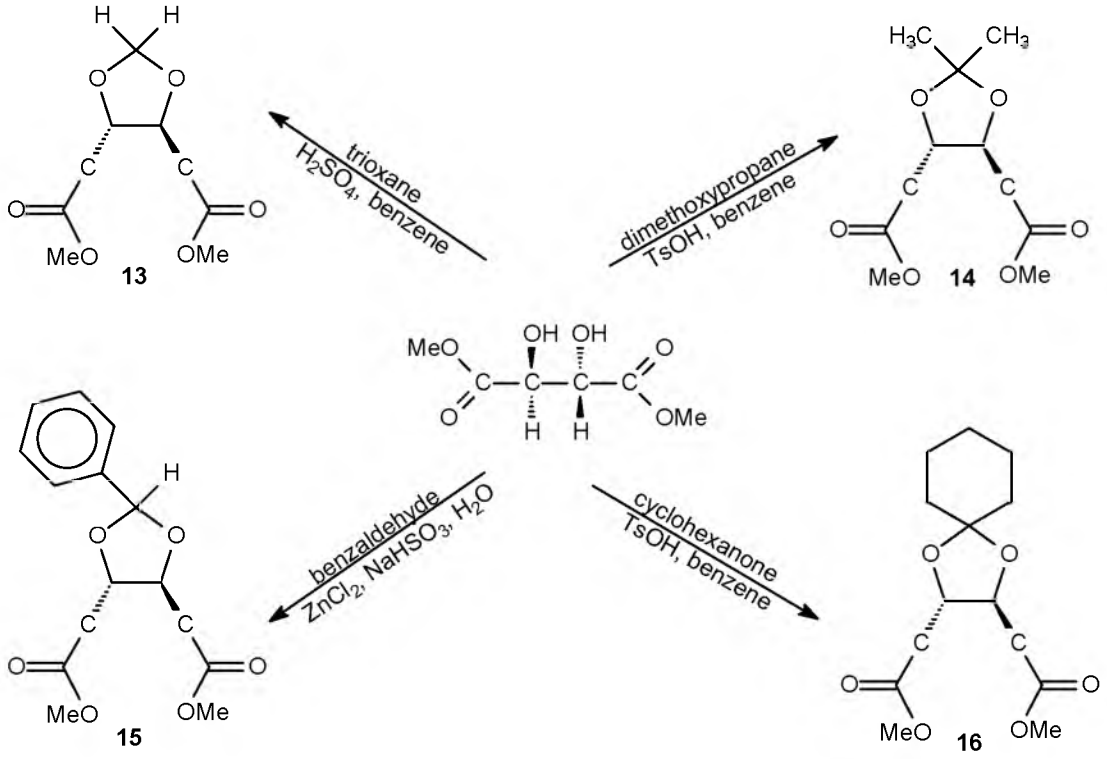
**Scheme 2.1:** Syntheses of Taddols

In the first reaction step, the dioxolane ring is formed, followed by the introduction of two diarylcarbinol groups. The general Taddol structure allows simple modification in both parts of the molecule, the aromatic as well as the dioxolane ring. The aromatic phenyls of the parent Taddol **1** can easily be replaced by a large variety of substituted phenyls or even other aromatics. Similarly, modifications in the dioxolane ring part, i.e. using aliphatic, aromatic, functionalised ketones or aldehydes, increase Taddol diversity. The different hosts should only slightly differ from each other in order to investigate the best achievable inclusion capabilities and to establish a relation between structure and resolution. As described in section 3.3.3, the vicinal diarylcarbinol groups are positioned perpendicular towards each other and are often

responsible for the formation of the crystal lattice. An increase in their size can lead to a different fit and thus a change in the crystal structure. This will, of course, influence the inclusion capability. On the other hand, a change in the dioxolane ring can also have a high impact on the inclusion capabilities since large parts of the guest compound are located at this position in the inclusion crystal. Thus, a broaden investigation of the Taddol's capabilities requires the development of an easy and fast synthesis.

### 2.3.2 Syntheses of dioxolane-dicarboxylates

The syntheses of Taddol-like compounds involve two reaction steps (see Scheme 2.1). Starting from dimethyl tartrates, the dioxolane-dicarboxylates (Scheme 2.2) can be synthesised in an acetalisation reaction, following known literature procedures.[17] In most cases this involves a simple, but time consuming reaction, as completion of the acetalisation varies from 8 hours to 4 days, depending on the respective substrate. Fortunately, a further purification of the dioxolane-dicarboxylates is unnecessary since they are pure enough to be used directly in the next synthetic step.




**Scheme 2.2:** Syntheses of dioxolane-dicarboxylates **13**-**16**

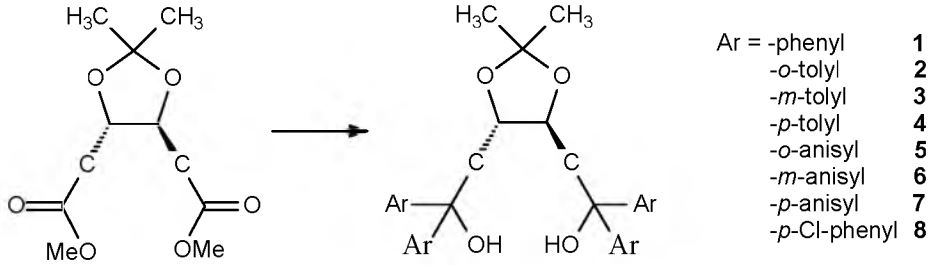
Four different dioxolane-dicarboxylates have been synthesised to attain structural variation in the dioxolane ring of the Taddol molecule.

It should be pointed out, that the use of unsymmetric ketones or aldehydes ($R^1 \neq R^2$, see

Scheme 2.1) does not lead to the formation of an additional chiral centre. Hence, an asymmetric dioxolane ring part does not create diastereomers. However, the $C_2$-symmetry of the traditional Taddols is lost and this may lead to new inclusion properties.

### 2.3.3 Syntheses of Taddols

The diarylcarbinol groups are introduced to the dioxolane-dicarboxylates *via Grignard* reactions (**A**) or *n*-butyl lithium halogen exchange reactions (**B**). Generally the yields in *Grignard* reactions vary from 15% to 75%. Several by-products can be formed which decrease the yield and aggravate the purification of the desired product. In most of the syntheses, the route *via* a *n*-butyl lithium halogen exchange reaction was preferred as it is more efficient. The desired compounds could be obtained in higher purities and reasonable yields up to 90%.
Whereas the first step of the Taddol syntheses offers the possibility to vary the dioxolane ring of the molecule, the introduction of the diarylcarbinol group in the second step allows the variation in the aromatic part.




**14**

| comp. | method | yield | $[\alpha]_D^{20}$ | mp | yield$_{(lit.)}$ | $[\alpha]_{D\ (lit.)}^{20}$ | mp$_{(lit.)}$ |
|---|---|---|---|---|---|---|---|
| 1 | B | 92% | -65 (1,$CHCl_3$) | 185°C | 74% | -65 (1,$CHCl_3$) | 193°C[12] |
| 2 | A<br>B | 39%<br>51% | -26 (0.4,$CHCl_3$) | 155°C | — | -33 (0.68,$CHCl_3$) | 162°C[3] |
| 3 | A<br>B | 28%<br>41% | -56 (1,$CHCl_3$) | 110°C | — | — | — |
| 4 | A<br>B | 45%<br>53% | -49 (1,$CHCl_3$) | 80°C | —<br>49% | -47 (0.12,$CHCl_3$)<br>-52 (1,$CHCl_3$) | 105°C[3]<br>105°C[12] |
| 5 | B | 55% | +134 (1,$CHCl_3$) | 223°C | 64% | +135 (1,$CHCl_3$) | 223°C[14] |
| 6 | A | 38% | -33 (0.2,$CHCl_3$) | 125°C | —% | — | — |
| 7 | A | 79% | -52 (1,$CHCl_3$) | 171°C | 68% | -59 (1,MeOH) | 171°C[14] |
| 8 | B | 73% | +90 (0.1,$CHCl_3$) | 180°C | 25% | -63 (1,MeOH) | 124°C[12] |

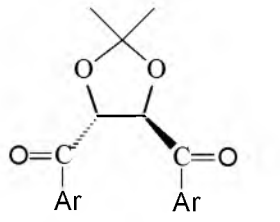
**Scheme 2.3:** Synthesis of Taddols 1-8

It should be noted, that deviations in melting points from literature examples can be due to the different methods of crystallisation used. Analytical and structural data, however, confirm that the structures have been identified correctly.

As mentioned earlier, a variety of Taddol-like compounds should be available to increase the diversity for the investigation of their inclusion and especially their resolution abilities. Compound **1** is the parent Taddol, which is also commercially available. Its synthesis is easy and the isolation of **1** from the crude reaction mixture was simply accomplished by the formation of inclusion crystals with methanol, dissolution in cyclohexane and azeotropic evaporation of the combined solvents.

With the syntheses of the bis-[di-(*o,m,p*)-tolylcarbinol]-derivatives, the size of the chiral cavities, which the Taddols are able to form in their crystal lattices, will be influenced. Thereby possibilities of the inclusion of larger guests may be created. Taddols **2** and **4** are known, but the synthesis of the third tolyl-derivative **3** is new. Purification of the di-*m*-tolylcarbinol-derivative by inclusion crystallisation with methanol is impossible. The first tendency of the *meta*-compound to be an inappropriate host compound (see chapter 3) has here taken shape. In contrast, the isolation of pure **2** and **4** was accomplished in a similar manner to the purification of Taddol **1**.

It should be noted, that the following by-product was formed during the synthesis of Taddol **4**.



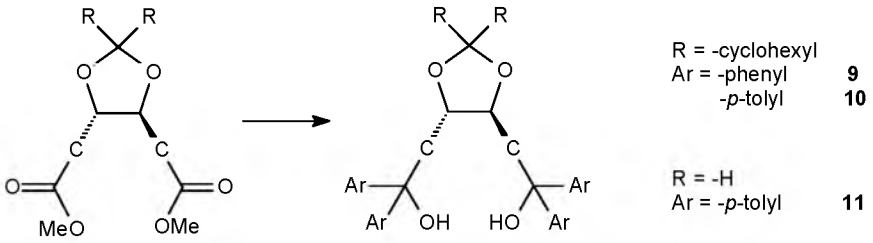

Ar = -*p*-tolyl

**Figure 2.6:** By-product in the synthesis of Taddol **4** (confirmed by X-ray)

Taddol **4** and its by-product can be separated by column chromatography.

With the syntheses of the bis-(*o,m,p*)-anisylcarbinol (**5**-**7**) and bis-*p*-chlorophenylcarbinol **8** derivatives, an extra functionality in the host molecule was introduced. The number of guest complexation sites should thus be increased. The syntheses and purifications of the *ortho* **5** as well as the *para*-compound **7** did not give any problems and were performed in a similar manner to Taddol **1**, but that of the *meta*-anisyl-Taddol **6** was more troublesome. In comparison with compound **3**, the purification by crystallisation with methanol was not possible. Instead, the Taddols **3** and **6** were obtained pure by column chromatography followed by crystallisation from heptane. Apparently, the low solubility of similar by-products as shown in Figure 2.6 prevented complete conversion to the carbinol.

The syntheses of Taddols, with a variation in the dioxolane ring part of the molecule is described in Scheme 2.4.

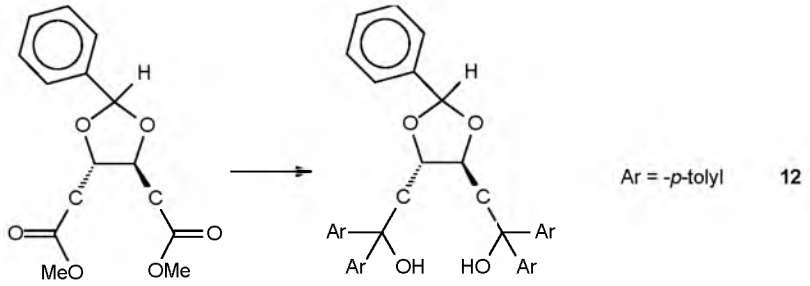



| comp. | method | yield | $[\alpha]_D^{20}$ | mp | yield$_{(lit.)}$ | $[\alpha]_{D\ (lit.)}^{20}$ | mp$_{(lit)}$ |
|---|---|---|---|---|---|---|---|
| 9 | B | 88% | -72 (1,$CHCl_3$) | 198°C | — | — | — |
| 10 | A | 42% | -65 (0.9,$CHCl_3$) | 195°C | — | — | — |
| 11 | B | 35% | -14 (0.9,$CHCl_3$) | 122°C | — | — | — |

**Scheme 2.4:** Syntheses of Taddols **9–11**

Taddol **10** and **11** are *para*-tolyl derivatives, whereas compound **9** with its diphenylcarbinol group is closely related to the parent Taddol **1**. Neither during their syntheses nor their purifications any problem was encountered. They can be obtained in high purity similar to **1**. Especially compound **1** has shown a great ability to act as host compound in inclusion resolution. Therefore an application of Taddol **9** in inclusion experiments is expected to deliver analogous results due to the highly similar structures. The results obtained in inclusion resolution experiments given in chapter 3 of this thesis, reveal that Taddol **4** is a good host. Therefore, a tolyl-group in the *para*-position is expected to play an important role in the inclusion abilities of the Taddols. With the compounds **10** and **11**, the influence of the *para*-tolyl-group can be studied in more detail, whereas with the Taddols **2** - **4** the effect of the aromatic substitution pattern can be demonstrated.

The last Taddol-like compound that has been synthesised is shown in the following scheme.




| comp. | method | yield | $[\alpha]_D^{20}$ | mp | yield$_{(lit.)}$ | $[\alpha]_{D\ (lit.)}^{20}$ | mp$_{(lit)}$ |
|---|---|---|---|---|---|---|---|
| 12 | B | 31% | +32 (0.2,$CHCl_3$) | 57°C | — | — | — |

**Scheme 2.5:** Synthesis of Taddol **12**

The synthesis and purification of **12** was performed without any problems. Taddol **12** is the only host molecule included in this research, whose symmetry is different. Whereas $C_2$-symmetry is predominantly present in all Taddol-based host molecules, compounds with $C_1$-symmetry are relatively rare. Taddol **12** offers, as it belongs to a different symmetry group, the possibility to analyse this influence on the inclusion abilities. As aromatic part, the *para*-tolylcarbinol group was chosen because of the previously mentioned reason.

### 2.3.4 Conclusions

Twelve different Taddol-like compounds have been synthesised. In general, their syntheses were facile, only in some cases the purification presented some problems. For an application of these compounds in inclusion resolution, their purity is essential, since inclusion crystallisation also deals with the problem of nucleation (see section 3.3.1). With compounds **1**, **2**, **4**, **5** and **7** - **12** a direct crystallisation of the methanol inclusion complex from the crude reaction mixture is possible after seeding. The seed crystals were obtained after column chromatography of a small amount of the respective crude reaction mixture. The almost pure compounds crystallise much easier with methanol to inclusion complexes. Only the *meta*-derivatives did not form any crystals at all with methanol. Generally, chromatography is a suitable method to separate the desired product from impurities. However, as the present reactions have also been performed on a relatively large scale of approximately 40 g, a different purification technique is favoured.
A variety of Taddol-based compounds has been synthesised, with related structural patterns. All of them represent possible host compounds. Due to their structural differences, the inclusion capabilities and optional conditions can be investigated. The application of mixtures of structurally related hosts is possible, allowing the Dutch Resolution concept as an approach to inclusion resolutions (see chapter 3).

## 2.4 Experimental section

*General Remarks*
$^1$H-NMR spectra were recorded on a Bruker AC-100 (100 MHz, FT) or a Bruker AC-300 spectrometer with tetramethylsilane as internal standard and WinNMR as software. IR spectra were run on a Perkin Elmer 298 spectrophotometer or Perkin Elmer FTIR 1720-X spectrophotometer with the program Winfirst. Elemental analyses were performed with a Carlo Erba instruments CHNSO 1108 elemental analyser. For mass spectroscopy, a double focusing VG 7070E was used. For the chemical ionisation (CI) technique, methane was used as reacting gas. GC/MS spectra were recorded on a Varian Saturn II using electron impact (EI) as ionisation method. GC-separation was carried out on a fused silica-capillary column (DB-5, 30 m x 0.25 mm, film thickness 0.25 μm). Melting points were measured on a Reichert Thermopan microscope (uncorrected) or on a Perkin Elmer DSC7 instrument. Optical rotations were determined on a Perkin Elmer 241 polarimeter at 589 nm, equipped with a quartz cell of 1.00 dm path length. The polarimeter was connected with a thermostat for exact temperature control and a recorder for continuous optical rotation measurements. GC was performed on a Hewlett-

Packard 5890 or 5890 Series II instrument, equipped with a capillary HP crosslinked methyl silicone (25 m x 0.31 mm) column, connected to a HP 5890 calculating integrator. Chiral GC was performed using a chiral B-DEX 120 capillary column (Supelco) or a WCOT Fused Silica 25mX0.25mm, CP Chirasil-Dex CB DF 25 m, Varian. DSC thermograms were recorded using a Perkin Elmer DSC7 instrument. Calibration was performed with In and Zn, Sn or Pb depending on the temperature range. Samples were prepared by the method described by Jaques, Collet and Wilen[16]. Samples were measured in stainless steel large volume pans (75 μl) or aluminium pans (30μl) at a rate of 10°C/min. HPLC was performed on a Shimadzu LC-10AD VP liquid chromatograph equipped with a reverse phase column by Alltech (Econosphere, C8, 5u, 0.46 cm Ø x 25 cm), a chiral Daicel Chiralcel OD-H column (25 x 0.46 cm, particle size: 5 μm) or a chiral Daicel Chiralcel OB column (25 x 0.46 cm, particle size: 5 μm) with filtered hexane/2-propanol mixtures as mobile phase. Detection was at 254 nm and the flow rate was 0.5 ml/min at ambient temperature. Class VP-5.0 was used as software. For column chromatography, the flash technique was used with silicagel 60H (Merck) as stationary phase and a pressure of about 1.5 bar. Thin layer chromatograms were run on glass supported silicagel 60 plates (0.25-layer, $F_{254}$, Merck). Compounds were detected using UV and oxidizing reagents, i.e. 5% $H_2SO_4$ in ethanol or a mixture of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (21 g), $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (1.8 g), water (469 ml) and 97% $H_2SO_4$ (31 ml). Dry solvents were obtained as follows: dichloromethane was distilled from phosphorous pentoxide. Diethyl ether was pre-dried on calcium chloride and distilled from calcium hydride. Hexane, benzene and dimethyl sulfoxide were distilled from calcium hydride. Triethylamine and phenylethylamine were distilled from potassium hydroxide. Tetrahydrofuran was distilled from lithium aluminium hydride, ethyl acetate from potassium hydrogen carbonate and 1,2-dimetoxyethane from sodium hydride. All other solvents and reagents were either p.a. or "reinst" quality and used as obtained from the supplier.
Systematic names were generated using a program provided by Advanced Chemistry Development Inc. (Toronto, Canada).

*Dimethyl 2,2-dimethyl-1,3-dioxolane-(4R,5R)-dicarboxylate*[17] **14**
A suspension of 10 g (56 mmol) (*R*,*R*)-dimethyltartrate, 8.9 g (84 mmol) dimethoxypropane and 121 mg (0.6 mmol) *p*-toluenesulfonic acid monohydrate in 200 ml benzene was heated to reflux with a soxhlet extractor for 26 hours. The molsieves (4 Å) were exchanged twice. After cooling to room temperature, 210 mg (1.5 mmol) potassium carbonate was added and stirring was continued for 2 hours. Then the reaction mixture was filtered, the benzene removed and the residue dissolved in ether (200 ml). This solution was washed with a saturated solution of $NaHCO_3$ in water, further with water and brine. Then dried over $MgSO_4$ and evaporated to a dark red, viscous oil which was suitable to use directly in the next reaction. (GC: purity 99 %). The yield was 12.1 g (98.5 %). $^1$H-NMR (100 MHz, $CDCl_3$): δ 4.82 (s, 2H, -C<u>H</u>), δ 3.83 (s, 6H, -OC<u>H</u>$_3$), δ 1.50 (s, 6H, -C<u>H</u>$_3$)

*Dimethyl 1,4-dioxaspiro[4.5]decane-(2R,3R)-dicarboxylate* **16**
A suspension of 20 g (112 mmol) (*R*,*R*)-dimethyltartrate, 46.6 ml (450 mmol) cyclohexanone, 0.7 g $ZnCl_2$ and 0.7 g *p*-toluenesulfonic acid monohydrate in 400 ml benzene was heated to reflux with a soxhlet extractor for one week. The molsieves (4 Å) were exchanged each day. After cooling to room temperature, 210 mg (1.5 mmol) potassium carbonate was added and stirring was continued for 2 hours. Then the reaction mixture was filtered, the benzene removed and the residue dissolved in ether (250 ml). This solution was washed with a saturated solution of $NaHCO_3$ in water, further with water and brine. Then dried over $MgSO_4$ and evaporated to a dark red, viscous oil. A colourless oil was obtained after vacuum distillation (2 torr, 100°C). (GC: purity 99 %). The yield was 20 g (82 %). $^1$H-NMR (100 MHz, $CDCl_3$): δ 4.82 (s, 2H, -C<u>H</u>), δ 3.82 (s, 6H, -OC<u>H</u>$_3$), δ 1.40 – 1.98 (m, 10H, -C<u>H</u>$_2$)

*Dimethyl 1,3-dioxolane-(4R,5R)-dicarboxylate* **13**[60]
A suspension of 5 g (28 mmol) (*R*,*R*)-dimethyltartrate, 2.5 g (28 mmol) trioxane and a catalytic amount of conc. $H_2SO_4$ in 100 ml benzene was heated to reflux with a soxhlet extractor for 2 days. The molsieves (4 Å) were exchanged twice. After cooling to room temperature, 210 mg (1.5 mmol) potassium carbonate was added and stirring was continued for 2 hours. Then the reaction mixture was filtered, the benzene removed and the residue dissolved in ether (150 ml). This solution was washed with a saturated solution of $NaHCO_3$ in water, further with water and brine. Then dried over $MgSO_4$ and evaporated to a dark oil (GC: purity 66 %). The yield was 4.1 g (78 %). $^1$H-NMR (100 MHz, $CDCl_3$): δ 5.19 (s, 2H, -C$\underline{H}_2$), δ 4.79 (s, 2H, -C$\underline{H}$), δ 3.82 (s, 6H, -OC$\underline{H}_3$)

*Dimethyl 2-phenyl-1,3-dioxolane-(4R,5R)-dicarboxylate* **15**
A suspension of 10 g (56 mmol) (*R*,*R*)-dimethyltartrate, 125 g (1.17 mol) benzaldehyde and 5 g $ZnCl_2$ were stirred at RT for 1 hour. While still stirring, a solution of 150 g $NaHSO_3$ in 1 l $H_2O$ was added. The precipitated crystals were filtered off and stirred in 750 ml $H_2O$ for 30 min, then again filtered off and stirred twice in 25 ml acetone. After filtration, 35 ml $H_2O$ was added to the filtrate. The ester **15** crystallised over night. After filtration, **15** was dried under vacuum. The yield was 12.1 g (81 %). $^1$H-NMR (100 MHz, $CDCl_3$): δ 7.50-7.25 (m, 5H, arom.), δ 5.95 (s, 1H, -C$\underline{H}$Ph), δ 4.85 (d, 1H, J=3.8, -C$\underline{H}$), δ 4.72 (d, 1H, J=3.8, -C$\underline{H}$), δ 3.79 (s, 6H, -OC$\underline{H}_3$)

*General procedure for a Grignard reaction* ***A***
The magnesium turnings were stirred in ether or THF under argon for one hour. After addition of catalytic amount of iodine, the suspension was heated to reflux. While still boiling, a solution of the respective bromoaryl reagent in ether or THF was added dropwise. The reaction mixture was kept boiling, until all magnesium turnings have reacted. A solution of the respective ester in ether or THF was added drop wise at 0°C, then the reaction mixture was heated to reflux for approximately 3 hours and stirred over night at RT. Then the reaction mixture was neutralised with saturated $NH_4Cl$ solution in water at 0°C. The water layer was extracted three times with diethyl ether. The combined organic layers were washed twice with brine, dried over $MgSO_4$ and evaporated to give the crude product.

*General procedure for a lithium exchange reaction* ***B***
A solution of the bromoaryl reagent in diethyl ether was added drop wise to *n*-butyl lithium (1.6 m in hexane) at -30°C under argon. The reaction mixture was then stirred at room temperature for 2 h and cooled again at -30°C, while a solution of the ester in diethyl ether was added slowly. The reaction mixture was warmed to room temperature and stirred over night. Then it was neutralised with saturated $NH_4Cl$ solution in water at 0°C. The water layer was extracted three times with diethyl ether. The combined organic layers were washed twice with brine, dried over $MgSO_4$ and evaporated to give the crude product.

*(4R,5R)-5-[hydroxy(diphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl(diphenyl)methanol* ***1***
Procedure **B**: 11.9 g (55 mmol) *dimethyl 2,2-dimethyl-1,3-dioxolane-(4R,5R)-dicarboxylate* **14**
33 ml (0.33 mol) bromobenzene in 100 ml diethyl ether
200 ml (0.33 mol) *n*-butyl lithium (1.6 m in hexane)
The crude product was chromatographed on silica gel, first with 200 ml $CH_2Cl_2$ followed by 400 ml of diethyl ether. The ether fraction yielded 24.2 g (94%) of **1** as a yellow foam. After recrystallisation in MeOH a 1:1 inclusion complex of **1** and MeOH was obtained. The yield was 24.0 g inclusion complex, thus 23.7 g **1** (92 %), ΔH=36.54 kJ/mol. Methanol was removed by azeotropic evaporation with cyclohexane and **1** was obtained as a white solid. Mp: 185 °C;

$[\alpha]_D^{20}$ = -65 (1,$CHCl_3$); $\Delta$H=15.29 kJ/mol, $^1$H-NMR (200 MHz, $CDCl_3$): $\delta$ 7.60-7.20 (m, 10H,arom.), $\delta$ 4.58 (s, 2H, -C<u>H</u>), $\delta$ 4.16 (s, 2H, -O<u>H</u>), $\delta$ 1.03 (s, 6H, -C<u>H</u>$_3$);IR: $\nu$ 3317 cm$^{-1}$ (-OH), $\nu$ 3057 cm$^{-1}$ (-$CH_{arom.}$), $\nu$ 2889 cm$^{-1}$ (-$CH_{methyl.}$), $\nu$ 1380 cm$^{-1}$ (-$CH_3$,symm.d.)

*(4R,5R)-(5-hydroxy[di(2-methylphenyl)]methyl-2,2-dimethyl-1,3-dioxolan-4-yl)[di(2-methylphenyl)]methanol* ***2***

Procedure **A**: 1.8 g (8.3 mmol) *dimethyl 2,2-dimethyl-1,3-dioxolane-(4R,5R)-dicarboxylate* **14**
8 ml (66.5 mmol) *ortho*-bromotoluene
1.62 g (66.5 mmol) magnesium turnings
50 ml diethyl ether

The crude product was chromatographed on silica gel, first with 50 ml $CH_2Cl_2$ followed by 100 ml of diethyl ether. The ether fraction yielded 0.08 g (2 %) of **2** as yellow foam.

Procedure **A***: 1 g (4.6 mmol) *dimethyl 2,2-dimethyl-1,3-dioxolane-(4R,5R)-dicarboxylate* **14** in 50 ml THF and 6.78 g (27.5 mmol) $CeCl_3$*
3.3 ml (27.5 mmol) *ortho*-bromotoluene
0.67 g (27.5 mmol) magnesium turnings
50 ml THF

The crude product was chromatographed on silica gel, first with 50 ml $CH_2Cl_2$ followed by 100 ml of diethyl ether. The ether fraction yielded 1.1 g (46 %) of **2** as yellow foam. After recrystallisation in MeOH a 1:1 inclusion complex of **2** and MeOH was obtained. The yield was 1 g inclusion complex, thus 0.94 g **2** (39 %). Mp: 119 °C; $\Delta$H=56.57kJ/mol, Elemental analysis for $C_{35}H_{38}O_4 \cdot CH_4O$: calc.C 77.95%, H 7.63%, found C 77.89%, H 7.21%.

Methanol was removed by azeotropic evaporation with cyclohexane and **2** was obtained as a white solid. Mp: 155 °C; $[\alpha]_D^{20}$ = -26 (c 0.4, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 7.79-7.77 (d, 4H, arom. $H_3$C-C-CH-C<u>H</u>, J = 6.8 Hz), $\delta$ 7.24-7.16 (m, 8H, arom.), $\delta$ 7.02-7.00 (d, 4H, arom. $H_3$C-C- C<u>H</u>, J = 5.3 Hz), $\delta$ 5.28 (s, 2H, -C<u>H</u>), $\delta$ 3.50 (s, 2H, -O<u>H</u>), $\delta$ 1.81 (br, 12H, Ph-C<u>H</u>$_3$), $\delta$ 1.55 (s, 6H, -C<u>H</u>$_3$); IR: $\nu$ 3288 cm$^{-1}$ (-OH), $\nu$ 3057 cm$^{-1}$ (-$CH_{arom.}$), $\nu$ 2881 cm$^{-1}$ (-$CH_{methyl.}$), $\nu$ 1380 cm$^{-1}$ (-$CH_3$,symm.d.), MS: ($\frac{m}{z}$) 523 ($M^+$)

Procedure **B**: 11.8 g (0.06 mol) *dimethyl 2,2-dimethyl-1,3-dioxolane-(4R,5R)-dicarboxylate* **14** in 100 ml diethyl ether
40.5 ml (0.28 mol) *ortho*-bromotoluene in 100 ml diethyl ether
200 ml (0.33 mol) *n*-butyl lithium (1.6 m in hexane)

The crude product was chromatographed on silica gel, first with 500 ml $CH_2Cl_2$ followed by 800 ml of diethyl ether. The ether fraction yielded 15.6 g (55 %) of **2** as yellow foam. After recrystallisation in MeOH a 1:1 inclusion complex of **2** and MeOH was obtained. The yield was 15.2 g inclusion complex, thus 14.3 g **2** (51 %).

*(4R,5R)-(5-hydroxy[di(3-methylphenyl)]methyl-2,2-dimethyl-1,3-dioxolan-4-yl)[di(3-methylphenyl)]methanol* ***3***

Procedure **A**: 3 g (14 mmol) *dimethyl 2,2-dimethyl-1,3-dioxolane-(4R,5R)-dicarboxylate* **14** in 50 ml diethyl ether
10 ml (82 mmol) *meta*-bromotoluene
2 g (82 mmol) magnesium turnings
50 ml diethyl ether

The crude product was chromatographed on silica gel (heptane/EtOAc 4:1), yielded in 2.4 g (34 %) of **3** as yellow foam. After recrystallisation from hexane pure **3** was obtained as a white

solid. The yield was 2.0 g (28 %). Mp: 110 °C; ΔH=26.84kJ/mol; $[\alpha]_D^{20}$ = -56 (c 1, $CHCl_3$), $^1$H-NMR (300 MHz, $CDCl_3$): δ 7.39-7.37 (d, 4H, arom. $H_3C$-C-C<u>H</u>, J = 7.8 Hz), δ 7.30-7.10 (m, 8H, arom.), δ 7.05-7.03 (d, 4H, arom. $H_3C$-C- C<u>H</u>-CH, J = 6.9 Hz), δ 4.57 (s, 2H, -C<u>H</u>), δ 3.79 (s, 2H, -O<u>H</u>), δ 2.33 (s, 6H, Ph-C<u>$H_3$</u>), δ 2.27 (s, 6H, Ph-C<u>$H_3$</u>), δ 1.06 (s, 6H, -C<u>$H_3$</u>); IR: ν 3312 $cm^{-1}$ (-OH), ν 3035 $cm^{-1}$ (-$CH_{arom.}$), ν 2882 $cm^{-1}$ (-$CH_{methyl.}$), ν 1377 $cm^{-1}$ (-$CH_3$,symm.d.), Elemental analysis for $C_{35}H_{38}O_4 \cdot CH_4O$: calc.C 77.95%, H 7.63%, found C 78.14%, H 7.54%; MS: ($\frac{m}{z}$) 523 ($M^+$)

Procedure **B**: 11.8 g (0.06 mol) *dimethyl 2,2-dimethyl-1,3-dioxolane-(4R,5R)-dicarboxylate* **14** in 100 ml diethyl ether
40.5 ml (0.33 mol) *meta*-bromotoluene in 100 ml diethyl ether
200 ml (0.33 mol) *n*-butyl lithium (1.6 m in hexane)
The crude product was dissolved in hexane and by seeding with crystals of pure **3**, 13.2 g **3** was obtained as a white solid (yield 41 %).

*(4R,5R)-(5-hydroxy[di(4-methylphenyl)]methyl-2,2-dimethyl-1,3-dioxolan-4-yl)[di(4-methylphenyl)]methanol* ***4***

Procedure **A**: 30 g (0.14 mol) *dimethyl 2,2-dimethyl-1,3-dioxolane-(4R,5R)-dicarboxylate* **14** in 200 ml diethyl ether
101.6 ml (0.84 mol) *para*-bromotoluene
20 g (0.84 mol) magnesium turnings
300 ml diethyl ether
The crude product was chromatographed on silica gel, first with 500 ml $CH_2Cl_2$ followed by 700 ml of diethyl ether. The ether fraction yielded 34.9 g (48.5 %) of **4** as a yellow foam. After recrystallisation in MeOH a 1:1 inclusion complex of **4** and MeOH was obtained. The yield was 35.1 g inclusion complex, thus 32.99 g **4** (45 %).
Mp: 116 °C; ΔH=55.26 kJ/mol; $^1$H-NMR (300 MHz, $CDCl_3$): δ 7.37-7.34 (d, 4H, arom. $H_3C$-C-CH-C<u>H</u>, J = 8.1 Hz), δ 7.22-7.19 (d, 4H, arom. $H_3C$-C-CH-C<u>H</u>, J = 8.1 Hz), δ 7.12-7.10 (d, 4H, arom. $H_3C$-C- C<u>H</u>, J = 8.3 Hz), δ 7.05-7.02 (d, 4H, arom. $H_3C$-C- C<u>H</u>, J = 8.3 Hz), δ 4.53 (s, 2H, -C<u>H</u>), δ 4.23 (s, 2H, -O<u>H</u>), δ 2.35 (s, 6H, Ph-C<u>$H_3$</u>), δ 2.28 (s, 6H, Ph-C<u>$H_3$</u>), δ 1.05 (s, 6H, -C<u>$H_3$</u>) and MeOH δ 3.38 (s, 3H, -C<u>$H_3$</u>), δ 1.17 (b, 1H, -OH);
Methanol was removed by azeotropic evaporation with cyclohexane and **4** was obtained as a white solid. Mp: 80 °C, $[\alpha]_D^{20}$ = -49 (c 1, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$): δ 7.37-7.34 (d, 4H, arom., $H_3C$-C-CH-C<u>H</u>, J = 8.1 Hz), δ 7.22-7.19 (d, 4H, arom. $H_3C$-C-CH-C<u>H</u>, J = 8.1 Hz), δ 7.12-7.10 (d, 4H, arom., $H_3C$-C- C<u>H</u>, J = 8.3 Hz), δ 7.05-7.02 (d,4H, arom. $H_3C$-C- C<u>H</u>, J = 8.3 Hz), δ 4.53 (s, 2H, -C<u>H</u>), δ 3.90 (s, 2H, -O<u>H</u>), δ 2.35 (s, 6H, Ph-C<u>$H_3$</u>), δ 2.28 (s, 6H, Ph-C<u>$H_3$</u>), δ 1.05 (s, 6H, -C<u>$H_3$</u>); ); IR: ν 3312 $cm^{-1}$ (-OH), ν 3035 $cm^{-1}$ (-$CH_{arom.}$), ν 2882 $cm^{-1}$ (-$CH_{methyl.}$), ν 1377 $cm^{-1}$ (-$CH_3$,symm.d.), Elemental analysis for $C_{35}H_{38}O_4 \cdot CH_4O$: calc.C 77.95%, H 7.63%, found C 78.14%, H 7.54%; MS: ($\frac{m}{z}$) 523 ($M^+$)

Procedure **B**: 10 g (0.05 mol) *dimethyl 2,2-dimethyl-1,3-dioxolane-(4R,5R)-dicarboxylate* **14** in 100 ml diethyl ether
34 ml (0.28 mol) *para*-bromotoluene in 100 ml diethyl ether
168 ml (0.28 mol) *n*-butyl lithium (1.6 m in hexane)
The crude product was dissolved in MeOH and by seeding with crystals of the 1:1 complex of **4** with MeOH, 14.2 g of this complex was obtained. The MeOH was then removed by refluxing a solution of the complex in benzene with a soxhlet extractor for 24 h. After removing the benzene and drying under reduced pressure **4** was obtained as a white solid (yield 53 %).

*(4R,5R)-(5-hydroxy[di(2-methoxyphenyl)]methyl-2,2-dimethyl-1,3-dioxolan-4-yl)[di(2-methoxyphenyl)]methanol* **5**

Procedure **B**: 10 g (0.05 mol) *dimethyl 2,2-dimethyl-1,3-dioxolane-(4R,5R)-dicarboxylate* **14** in 100 ml diethyl ether
34 ml (0.28 mol) *ortho*-bromotoluene in 100 ml diethyl ether
168 ml (0.28 mol) *n*-butyl lithium (1.6 m in hexane)

The crude product was chromatographed on silica gel, first with 200 ml $CH_2Cl_2$ followed by 300 ml of diethyl ether. The ether fraction yielded 15.2 g (56 %) of **5** as yellow foam. After recrystallisation in MeOH a 1:1 inclusion complex of **5** and MeOH was obtained. The yield was 15.85 g inclusion complex, thus 14.9 g **5** (55 %). Mp (with MeOH): 152°C; $\Delta$H (with MeOH)= 13.27 kJ/mol; Mp: 223 °C; $[\alpha]_D^{20}$ = +134 (c 0.2, $CHCl_3$).

Methanol was removed by azeotropic evaporation with cyclohexane and **5** was obtained as a white solid. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 7.96-7.93 (dd, 2H, arom., $J_1$ = 7.8 Hz, $J_2$ = 1.8 Hz), $\delta$ 7.72-7.69 (dd, 2H, arom., $J_1$ = 7.8 Hz, $J_2$ = 1.8 Hz), $\delta$ 7.11-7.05 (td, 2H, arom., $J_1$ = 7.5 Hz, $J_2$ = 1.2), $\delta$ 6.96-6.90 (td, 2H, arom., $J_1$ = 7.5 Hz, $J_2$ = 1.2), $\delta$ 7.00-6.71 (m, 4H, arom.), $\delta$ 6.69-6.65 (dd, 2H, arom., $J_1$ = 8.1 Hz, $J_2$ = 1.2), $\delta$ 5.92-5.89 (dd, 2H, arom., $J_1$ = 7.8 Hz, $J_2$ = 1.5), $\delta$ 5.67 (d, 2H, -C<u>H</u>, J=2.7), $\delta$ 5.24 (d, 2H, -O<u>H</u>, J=2.7), $\delta$ 3.36 (s, 6H, Ph-CO<u>H</u>$_3$), $\delta$ 3.11 (s, 6H, Ph-CO<u>H</u>$_3$), $\delta$ 1.58 (s, 6H, -C<u>H</u>$_3$); IR: $\nu$ 3504 cm$^{-1}$ (-OH), $\nu$ 2975 cm$^{-1}$ (-$CH_{arom.}$), $\nu$ 2931 cm$^{-1}$ (-$CH_{methyl}$), $\nu$ 2832 cm$^{-1}$ (-$OCH_3$), $\nu$ 1371 cm$^{-1}$ (-$CH_3$,symm.d.), MS: ($\frac{m}{z}$) 587 ($M^+$); Elemental analysis for $C_{35}H_{38}O_8$: calc.C 71.65%, H 6.53%, found C 71.49%, H 6.53%.

*(4R,5R)-(5-hydroxy[di(3-methoxyphenyl)]methyl-2,2-dimethyl-1,3-dioxolan-4-yl)[di(3-methoxyphenyl)]methanol* **6**

Procedure **A**: 10 g (46 mmol) *dimethyl 2,2-dimethyl-1,3-dioxolane-(4R,5R)-dicarboxylate* **14** in 100 ml diethyl ether
34.4 ml (276 mmol) *meta*-bromoanisole
6.7 g (276 mmol) magnesium turnings
150 ml diethyl ether

The crude product was chromatographed on silica gel, first with 200 ml $CH_2Cl_2$ followed by 300 ml of diethyl ether. The ether fraction yielded 10.3 g (38 %) of **6** as yellow foam.

Mp: 125°C; $[\alpha]_D^{20}$ = -33 (c 0.2, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 7.27-7.21 (m, 2H, arom.), $\delta$ 7.20-7.14 (m, 4H, arom.), $\delta$ 7.10-7.09 (t, 2H, arom., J = 14.0 Hz), $\delta$ 6.96-6.93 (m, 4H, arom.), $\delta$ 6.85-6.81 (dd, 2H, arom., $J_1$ = 8.1 Hz, $J_2$ = 0.9 Hz), $\delta$ 6.77-6.73 (dd, 2H, arom., $J_1$ = 8.1 Hz, $J_2$ = 0.9 Hz), $\delta$ 4.57 (s, 2H, -C<u>H</u>), $\delta$ 3.92 (s, 2H, -O<u>H</u>), $\delta$ 3.76 (s, 6H, Ph-CO<u>H</u>$_3$), $\delta$ 3.70 (s, 6H, Ph-CO<u>H</u>$_3$), $\delta$ 1.10 (s, 6H, -C<u>H</u>$_3$); ); IR: $\nu$ 3345 cm$^{-1}$ (-OH), $\nu$ 2975 cm$^{-1}$ (-$CH_{arom.}$), $\nu$ 2930 cm$^{-1}$ (-$CH_{methyl}$), $\nu$ 2833 cm$^{-1}$ (-$OCH_3$), $\nu$ 1371 cm$^{-1}$ (-$CH_3$,symm.d.), MS: ($\frac{m}{z}$) 586; Elemental analysis for $C_{35}H_{38}O_8$: calc.C 71.65%, H 6.53%, found C 72.06%, H 6.68%.

*(4R,5R)-(5-hydroxy[di(4-methoxyphenyl)]methyl-2,2-dimethyl-1,3-dioxolan-4-yl)[di(4-methoxyphenyl)]methanol* **7**

Procedure A: 10 g (46 mmol) *dimethyl 2,2-dimethyl-1,3-dioxolane-(4R,5R)-dicarboxylate* **14** in 100 ml diethyl ether
34.4 ml (276 mmol) *para*-bromoanisole
6.7 g (276 mmol) magnesium turnings
150 ml diethyl ether

The crude product was chromatographed on silica gel, first with 200 ml $CH_2Cl_2$ followed by 300 ml of diethyl ether. The ether fraction yielded 22.3 g (83 %) of **7** as yellow foam, from

which, after diggeration in MeOH a 1:1 inclusion complex of **7** and MeOH was obtained. The yield was 22.4 g (79 %).

Mp: 102°C; ΔH=51.14kJ/mol; $^1$H-NMR (300 MHz, $CDCl_3$): δ 7.45-7.42 (d, 4H, arom. $H_3OC$-C-CH-C<u>H</u>, J = 8.8Hz), δ 7.25-7.22 (d, 4H, arom. $H_3OC$-C-CH-C<u>H</u>, J = 9.0 Hz), δ 6.87-6.84 (d, 4H, arom. $H_3OC$-C- C<u>H</u>, J = 8.8 Hz), δ 6.78-6.75 (d, 4H, arom. $H_3OC$-C- C<u>H</u>, J = 8.3 Hz), δ 4.46 (s, 2H, -C<u>H</u>), δ 4.22 (s, 2H, -O<u>H</u>), δ 3.82 (s, 6H, Ph-CO<u>H</u>$_3$), δ 3.75 (s, 6H, Ph-CO<u>H</u>$_3$), δ 1.06 (s, 6H, -C<u>H</u>$_3$) and MeOH δ 3.38 (s, 3H, -C<u>H</u>$_3$), δ 1.61 (b, 1H, -OH)

Methanol was removed by azeotropic evaporation with cyclohexane and **7** was obtained as a white solid. Mp: 171°C; $[\alpha]_D^{20}$ = -52 (c 0.99, $CHCl_3$); ΔH=39.44 kJ/mol; IR: ν 3303 cm$^{-1}$ (-OH), ν 2960 cm$^{-1}$ (-$CH_{arom.}$), ν 2914 cm$^{-1}$ (-$CH_{methyl.}$), ν 2847 cm$^{-1}$ (-$OCH_3$), ν 1370 cm$^{-1}$ (-$CH_3$,symm.d.), MS: ($\frac{m}{z}$) 587 ($M^+$); Elemental analysis for $C_{35}H_{38}O_8$: calc.C 71.65%, H 6.53%, found C 71.52%, H 6.59%.

*(4R,5R)-di(4-chlorophenyl)5-[di(4-chlorophenyl)(hydroxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl-methanol* **8**

Procedure B: 7.1 g (0.032 mol) *dimethyl 2,2-dimethyl-1,3-dioxolane-(4R,5R)-dicarboxylate* **14** in 80 ml THF
30.63 g (0.16 mol) *para*-chlorobromobenzene in 80 ml THF
100 ml (0.16 mol) *n*-butyl lithium (1.6 m in hexane)

The crude product was chromatographed on silica gel, first with 100 ml $CH_2Cl_2$ followed by 200 ml of diethyl ether. The ether fraction yielded 15.6 g (81 %) of **8** as yellow foam, from which pure **8** was obtained after crystallisation from hexane. The yield was 14.1 g (73 % **8**).

Mp: 180°C; $[\alpha]_D^{20}$ = +90(c 0.1, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$): δ 7.75-7.71 (dt, 2H, arom., $J_1$ = 9.3 Hz, $J_2$ = 2.4), δ 7.52-7.47 (dt, 2H, arom., $J_1$ = 9.3 Hz, $J_2$ = 2.4), δ 7.38-7.25 (m, 10H, arom.), δ 6.78-6.75 (dt, 2H, arom., $J_1$ = 9.3 Hz, $J_2$ = 2.4), δ 5.69-5.67 (d, 2H, -C<u>H</u>$_2$, J = 6.3), δ 4.99-4.97 (d, 2H, -O<u>H</u>, J = 6.3), δ 1.38 (s, 6H, -C<u>H</u>$_3$); ); IR: ν 3479 cm$^{-1}$ (-OH), ν 2965 cm$^{-1}$ (-$CH_{arom.}$), ν 2920 cm$^{-1}$ (-$CH_{methyl.}$), ν 1373 cm$^{-1}$ (-$CH_3$,symm.d.), ν 1090 cm$^{-1}$ (-CCl); MS: ($\frac{m}{z}$) 309 $CH_3COCHCOH(C_6H_4Cl)_2$+1, 293 $COCHCOH(C_6H_4Cl)_2$, 265 $CHCOH(C_6H_4Cl)_2$, 251 $COH(C_6H_4Cl)_2$, 139 $COHC_6H_4Cl$-1, 111 $C_6H_4Cl$ -1; Elemental analysis for $C_{31}H_{26}Cl_4O_4$: calc. C 61.61%, H 4.34%, found C 61.21%, H 4.61%.

*(2R,3R)-3-[hydroxy(diphenyl)methyl]-1,4-dioxaspiro[4.5]dec-2-yl(diphenyl)methanol* **9**

Procedure **B**: 14.2 g (55 mmol) *dimethyl 1,4-dioxaspiro[4.5]decane-(2R,3R)-dicarboxylate* **16** in 80 ml THF
33 ml (0.33 mol) bromobenzene in 100 ml diethyl ether
200 ml (0.33 mol) *n*-butyl lithium (1.6 m in hexane)

The crude product was chromatographed on silica gel, first with 200 ml $CH_2Cl_2$ followed by 400 ml of diethyl ether. The ether fraction yielded 24.3 g (88%) of **9** as a yellow foam. After recrystallisation in MeOH a 1:1 inclusion complex of **9** and MeOH was obtained. Methanol was removed by azeotropic evaporation with cyclohexane and **9** was obtained as a white solid.

Mp: 198°C; $[\alpha]_D^{20}$ = -72 (c 1, $CHCl_3$); ΔH=39.94 kJ/mol; $^1$H-NMR (300 MHz, $CDCl_3$): δ 7.53-7.23 (m, 20H, arom.), δ 4.56 (s, 2H, -C<u>H</u>), δ 3.92 (s, 2H, -O<u>H</u>), δ 1.44-1.40 (m, 10H, -C<u>H</u>$_2$); IR: ν 3320 cm$^{-1}$ (-OH), ν 2974 cm$^{-1}$ (-$CH_{arom.}$), ν 2932 cm$^{-1}$ (-$CH_{methyl}$), ν 1445 cm$^{-1}$ (-$CH_2$)

*(2R,3R)-(3-hydroxy[di(4-methylphenyl)]methyl-1,4-dioxaspiro[4.5]dec-2-yl)[di(4-methylphenyl)] methanol* **10**

Procedure **B**: 7.04 g (27 mmol) *dimethyl 1,4-dioxaspiro[4.5]decane-(2R,3R)-dicarboxylate* **16** in 80 ml THF
20.4 ml (0.17 mol) *para*-bromotoluene in 100 ml diethyl ether
101 ml (0.28 mol) *n*-butyl lithium (1.6 m in hexane)

The crude product was chromatographed on silica gel, first with 200 ml $CH_2Cl_2$ followed by 300 ml of diethyl ether. The ether fraction yielded 8.6 g (56 %) of **10** as yellow foam. After recrystallisation in MeOH a 1:1 inclusion complex of **10** and MeOH was obtained. Methanol was removed by azeotropic evaporation with cyclohexane and **10** was obtained as a white solid (6.4 g, 42%).

$\Delta$H=26.71 kJ/mol; Mp: 195°C; $[\alpha]_D^{20}$ = -65 (c 0.9, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 7.39-7.37 (d, 4H, arom., J = 8.1 Hz), $\delta$ 7.26-7.24 (d, 4H, arom., J = 8.1), $\delta$ 7.10-7.08 (d, 4H, arom., J = 8.1 Hz), $\delta$ 7.07-7.04 (d, 4H, arom., J = 8.1 Hz), $\delta$ 4.51 (s, 2H, -C<u>H</u>), $\delta$ 3.90 (s, 2H, -O<u>H</u>), $\delta$ 2.35 (s, 6H, Ph-C<u>H</u>$_3$), $\delta$ 2.29 (s, 6H, Ph-C<u>H</u>$_3$), $\delta$ 1.46-1.14 (m, 10H, -C<u>H</u>$_2$); ); IR: $\nu$ 3317 cm$^{-1}$ (-OH), $\nu$ 3025 cm$^{-1}$ (-$CH_{arom.}$), $\nu$ 2931 cm$^{-1}$ (-$CH_{methyl}$), $\nu$ 1445 cm$^{-1}$ (-$CH_2$)$\nu$ 1365 cm$^{-1}$ (-$CH_3$,symm.d.), Elemental analysis for $C_{38}H_{42}O_4$: calc.C 81.11%, H 7.52%, found C 81.04%, H 7.62%; MS: ($\frac{m}{z}$) 562

*(4R,5R)-(5-hydroxy[di(4-methylphenyl)]methyl-1,3-dioxolan-4-yl)[di(4-methylphenyl)] methanol* **11**

Procedure **B**: 5.2 g (27 mmol) *dimethyl 1,3-dioxolane-(4R,5R)-dicarboxylate* **13**
20.4 ml (0.17 mol) *para*-bromotoluene in 100 ml diethyl ether
101 ml (0.28 mol) *n*-butyl lithium (1.6 m in hexane)

The crude product was chromatographed on silica gel, first with 100 ml $CH_2Cl_2$ followed by 200 ml of diethyl ether. The ether fraction yielded 7.0 g (52 %) of **11** as a yellow foam, from which pure **11** was obtained after crystallisation from hexane. The yield was 4.7 g (35 %) **11**.

Mp: 122°C; $[\alpha]_D^{20}$ = +14(c 0.9, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 7.38-7.35 (d, 4H, arom., J = 8.3 Hz), $\delta$ 7.16-7.13 (d, 4H, arom., J = 8.3), $\delta$ 7.12-7.09 (d, 4H, arom., J = 8.3 Hz), $\delta$ 6.95-6.93 (d, 4H, arom., J = 8.3 Hz), $\delta$ 5.03 (s, 2H, -C<u>H</u>), $\delta$ 4.76 (s, 2H, -O<u>H</u>), $\delta$ 2.52 (s, 2H, -C<u>H</u>$_2$); $\delta$ 2.31 (s, 6H, Ph-C<u>H</u>$_3$), $\delta$ 2.26 (s, 6H, Ph-C<u>H</u>$_3$); IR: $\nu$ 3375 cm$^{-1}$ (-OH), $\nu$ 3026 cm$^{-1}$ (-$CH_{arom.}$), $\nu$ 2921 cm$^{-1}$ (-$CH_{methyl.}$), $\nu$ 1450 cm$^{-1}$ (-$CH_2$), $\nu$ 1408 cm$^{-1}$ (-$CH_2$), Elemental analysis for $C_{33}H_{34}O_4$: calc. C 80.13%, H 6.93%, found C 81.06%, H 7.15%; MS: ($\frac{m}{z}$) 494

*(4R,5R)-(5-hydroxy[di(4-methylphenyl)]methyl-2-phenyl-1,3-dioxolan-4-yl)[di(4-methylphenyl)] methanol* **12**

Procedure **B**: 1.5 g (6 mmol) *dimethyl 2-phenyl-1,3-dioxolane-(4R,5R)-dicarboxylate* **15**
4 ml (43 mmol) *para*-bromotoluene in 20 ml diethyl ether
20 ml (43 mmol) *n*-butyl lithium (1.6 m in hexane)

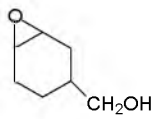
The crude product was chromatographed on silica gel, first with 30 ml $CH_2Cl_2$ followed by 100 ml of diethyl ether. The ether fraction yielded 1.7 g (49 %) of **11** as a yellow foam, from which pure **11** was obtained after crystallisation from hexane. The yield was 1.1 g (31 %) **11**.

Mp: 57°C; $[\alpha]_D^{20}$ = +32(c 0.2, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$: $\delta$ 7.52-7.39 (m, 5H, arom.), $\delta$ 7.33-7.30 (d, 4H, arom., J = 8.0 Hz), $\delta$ 7.21-7.18 (d, 4H, arom., J = 8.0 Hz), $\delta$ 7.15-7.11 (d, 4H, arom., J = 8.0 Hz), $\delta$ 7.08-7.01 (d, 4H, arom., J = 8.0 Hz), $\delta$ 5.85 (s, 1H, -C<u>H</u>Ph), $\delta$ 4.86 (d, 1H, J=3.7, -C<u>H</u>), $\delta$ 4.74 (d, 1H, J=3.7, -C<u>H</u>), $\delta$ 4.60 (s, 2H, -O<u>H</u>), $\delta$ 2.33 (s, 6H, Ph-C<u>H</u>$_3$), $\delta$ 2.26 (s, 6H, Ph-C<u>H</u>$_3$); IR: $\nu$ 3393 cm$^{-1}$ (-OH), $\nu$ 3008 cm$^{-1}$ (-$CH_{arom.}$), $\nu$ 2927 cm$^{-1}$ (-$CH_{methyl}$); MS: ($\frac{m}{z}$)

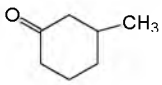
447 ($CHCOH(C_6H_4CH_3)_2)_2$, 211 $COH(C_6H_4CH_3)_2$ +1, 195 $C(C_6H_4CH_3)_2$ +1, 134 $CCOHC_6H_4CH_3$, 119 $C_6H_4CH_3$ –1, 105 $CC_6H_4CH_3$ +1, 91 $C_6H_4CH_3$ –1, 77 $C_6H_4$ +1; Elemental analysis for $C_{39}H_{38}O_4$: calc.C 82.08%, H 6.71%, found C 80.83%, H 7.58%

## 2.5 Appendix

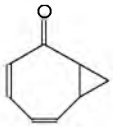
The following survey shows all racemates resolved by Toda and co-workers. Results are given as *e.e.*%.



*e.e.* 49 %
**G1**

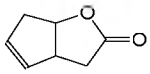


*e.e.* 15 %
**G2**

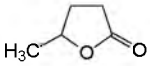


*e.e.* 10 %
**G3**

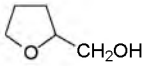
*e.e.* 9 %
**G4**



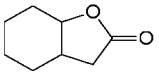
*e.e.* 1 %
**G5**



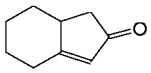
*e.e.* 14 %
**G6**



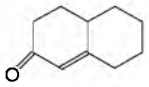
*e.e.* 21 %
**G7**



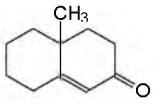
*e.e.* 23 %
**G8**



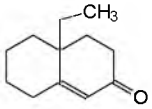
*e.e.* 100 %
**G9**



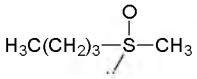
*e.e.* 100 %
**G10**



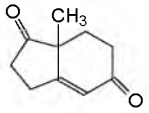
*e.e.* 100 %
**G11**



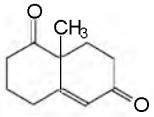
*e.e.* 100 %
**G12**



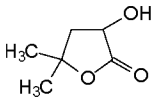
*e.e.* 4 %
**G13**



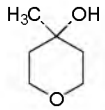
*e.e.* 100 %
**G14**



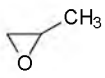
*e.e.* 100 %
**G15**



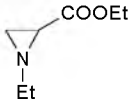
*e.e.* 74 %
**G16**



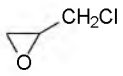
*e.e.* 43 %
**G17**



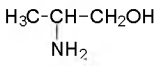
*e.e.* 52-70 %
**G18**



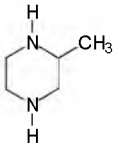
*e.e.* 64-100%
**G19**



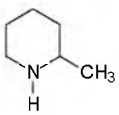
*e.e.* 55 %
**G20**



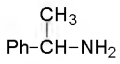
*e.e.* 65-69 %
**G21**



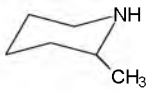
*e.e.* 82 %
**G22**



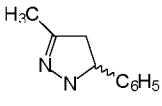
*e.e.* 24 %
**G23**



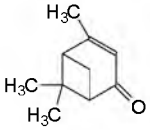
*e.e.* 91 %
**G24**



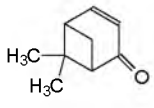
*e.e.* 42 %
**G25**



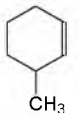
*e.e.* 96 %
**G26**



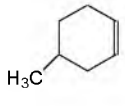
*e.e.* 99 %
**G27**



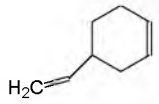
*e.e.* 94 %
**G28**



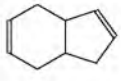
*e.e.* 13-100 %
**G29**



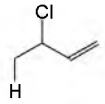
*e.e.* 3-75 %
**G30**



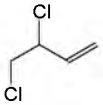
*e.e.* 8-28 %
**G31**



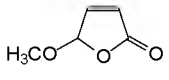
n.d.
**G32**



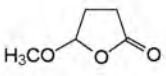
*e.e.* 4-56 %
**G33**



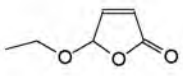
n.d.
**G34**



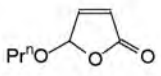
*e.e.* 92 %
**G35**



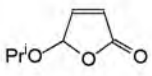
*e.e.* 96 %
**G36**



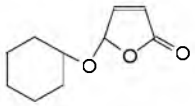
*e.e.* 88-100 %
**G37**



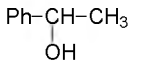
*e.e.* 2-94 %
**G38**



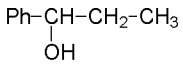
*e.e.* 82-90 %
**G39**



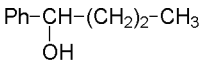
*e.e.* 92 %
**G40**



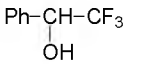
*e.e.* 95-98 %
**G41**



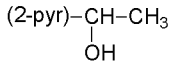
*e.e.* 62-100 %
**G42**



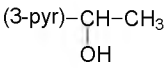
no compl.
**G43**



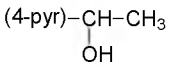
no compl.
**G44**



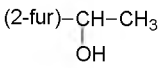
*e.e.* 76-99 %
**G45**



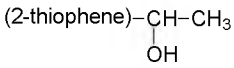
*e.e.* 0-99 %
**G46**



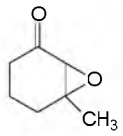
*e.e.* 0-77 %
**G47**



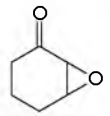
*e.e.* 93 %
**G48**



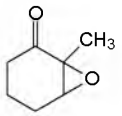
*e.e.* 86 %
**G49**



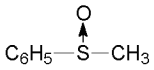
*e.e.* 97-100 %
**G50**



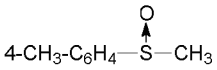
*e.e.* 75-100 %
**G51**



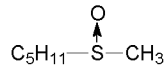
*e.e.* 63 %
**G52**



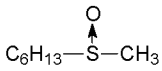
*e.e.* 57 %
**G53**



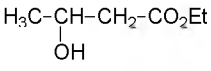
*e.e.* 98 %
**G54**



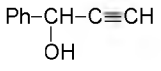
*e.e.* 96 %
**G55**



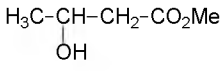
*e.e.* 49 %
**G56**



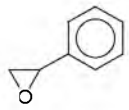
*e.e.* 78 %
**G57**



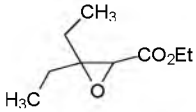
*e.e.* 92-100 %
**G58**



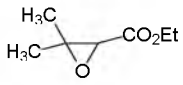
*e.e.* 80 %
**G59**



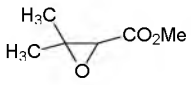
*e.e.* 47-75 %
**G60**



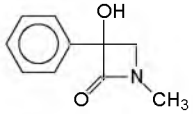
*e.e.* 100 %
**G61**



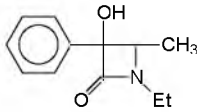
*e.e.* 100 %
**G62**



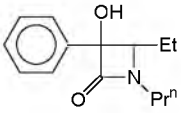
*e.e.* 70-86 %
**G63**



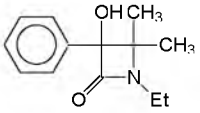
*e.e.* 41-85 %
**G64**



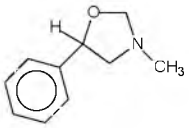
*e.e.* 57-85 %
**G65**



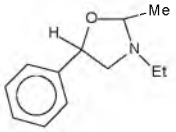
*e.e.* 16-52 %
**G66**



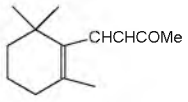
*e.e.* 81-90 %
**G67**



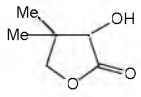
*e.e.* 42-45 %
**G68**



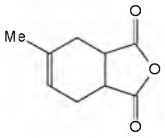
*e.e.* 24-64 %
**G69**



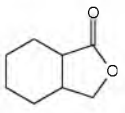
**G70**



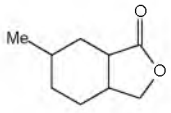
*e.e.* 99 %
**G71**



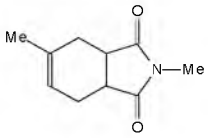
*e.e.* 100 %
**G72**



*e.e.* 67 %
**G73**



*e.e.* 100 %
**G74**



*e.e.* 0-100 %
**G75**



*e.e.* 27-100 %
**G76**



*e.e.* 100 %
**G77**



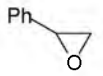
*e.e.* 46-100 %
**G78**



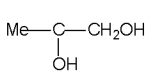
*e.e.* 54-100 %
**G79**



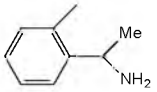
*e.e.* 100 %
**G80**



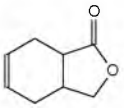

*e.e.* 90 %
**G81**



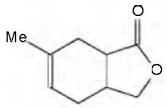

*e.e.* 90 %
**G82**



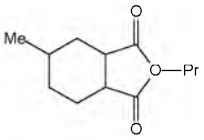

*e.e.* 95 %
**G83**



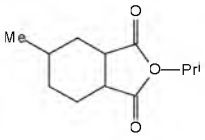

*e.e.* 43 %
**G84**




*e.e.* 100 %
**G85**




*e.e.* 52-98 %
**G86**




*e.e.* 50-98 %
**G87**

**Figure 2.7:** Racemic guest compounds used by Toda and co-workers

Additional data and results of Toda's resolutions are summarised in the table below.

| entry | host | guest | method | product | host:guest | yield % | *e.e.* % | S |
|---|---|---|---|---|---|---|---|---|
| 1 | A | G1 | crystal. | | | | 49 | |
| 2 | A | G2 | crystal. | | | | 15 | |
| 3 | A | G3 | crystal. | | | | 10 | |
| 4 | A | G4 | crystal. | | | | 9 | |
| 5 | A | G5 | crystal. | | | | 1.3 | |
| 6 | A | G6 | crystal. | | | | 14 | |
| 7 | A | G7 | crystal. | | | | 21 | |
| 8 | A | G8 | crystal. | | | | 23 | |
| 9 | A | G9 | crystal. | + | | 80 | 100 | 0.8 |
| 10 | A | G10 | crystal. | - | | 41 | 100 | 0.4 |
| 11 | A | G11 | crystal. | - | | 62 | 100 | 0.6 |
| 12 | A | G12 | crystal. | - | | 43 | 100 | 0.4 |
| 13 | A | G13 | crystal. | | | | 4 | |
| 14 | A | G14 | crystal. | - | | 58 | 100 | 0.6 |
| 15 | A | G15 | crystal. | - | | 70 | 100 | 0.7 |
| 16 | E | G16 | crystal. | - | | | 74 | |
| 17 | E | G17 | crystal. | - | | | 43 | |
| 18 | E | G18 | crystal. | + | | | 52 | |
| 19 | D | G18 | crystal. | + | | | 70 | |
| 20 | E | G19 | crystal. | - | | | 100 | |
| 21 | D | G19 | crystal. | + | | | 64 | |
| 22 | D | G20 | crystal. | - | | | 55 | |
| 23 | E | G21 | crystal. | + | | | 69 | |
| 24 | E | G21 | fract.dist. | + | | 37 | 100 | 0.4 |
| 25 | D | G21 | fract.dist. | + | | 33 | 100 | 0.3 |
| 26 | D | G21 | crystal. | + | | | 65 | |
| 27 | D | G22 | crystal. | + | | | 82 | |
| 28 | D | G23 | crystal. | + | | | 24 | |
| 29 | A | G23 | fract.dist. | + | | 98 | 42 | 0.4 |
| 30 | A | G24 | crystal. | - | 2:1 | 62 | 91 | 0.6 |
| 31 | A | G24 | fract.dist. | - | | 3 | 62 | 0 |

| entry | host | guest | method | product | host:guest | yield % | *e.e.* % | S |
|---|---|---|---|---|---|---|---|---|
| 32 | D | G25 | crystal. | + | 1:1 | 90 | 42 | 0.4 |
| 33 | B | G26 | crystal. | *S* | 1:1 | 42 | 96 | 0.4 |
| 34 | B | G27 | crystal. | - | 1:1 | 48 | 99 | 0.5 |
| 35 | A | G28 | crystal. | + | 1:1 | 47 | 94 | 0.4 |
| 36 | D | G29 | crystal. | - | 2:1 | 66 | 75 | 0.5 |
| 37 | D | G29 | sorpt. | - | 2:1 | 86 | 13 | 0.1 |
| 38 | D | G29 | fract.dist. | + | | 9 | 100 | 0.1 |
| 39 | D | G30 | crystal. | + | | 66 | 75 | 0.5 |
| 40 | D | G30 | sorpt. | + | | 82 | 3 | 0 |
| 41 | D | G30 | fract.dist. | - | | 100 | 3 | 0 |
| 42 | D | G31 | crystal. | - | | 73 | 28 | 0.2 |
| 43 | D | G31 | sorpt. | - | | 64 | 8 | 0.1 |
| 44 | D | G32 | crystal. | - | | 90 | n.d. | |
| 45 | D | G32 | sorpt. | - | | 53 | n.d. | |
| 46 | D | G33 | crystal. | - | | 48 | 56 | 0.3 |
| 47 | D | G33 | sorpt. | - | | 65 | 4 | 0 |
| 48 | D | G33 | fract.dist. | + | | 104 | 4 | 0 |
| 49 | D | G34 | crystal. | + | | 42 | n.d. | |
| 50 | D | G34 | sorpt. | + | | 71 | n.d. | |
| 51 | D | G34 | fract.dist. | - | | 85 | n.d. | |
| 52 | E | G35 | crystal. | + | | 91 | 18 | 0.2 |
| 53 | E | G35 | sorpt. | n. comp. | | | | |
| 54 | B | G35 | crystal. | - | | 41 | 92 | 0.4 |
| 55 | B | G35 | sorpt. | n. comp. | | | | |
| 56 | B | G36 | crystal. | - | | 50 | 96 | 0.5 |
| 57 | B | G36 | sorpt. | n. comp. | | | | |
| 58 | E | G37 | crystal. | + | | 32 | 88 | 0.3 |
| 59 | E | G37 | sorpt. | + | | 24 | 98 | 0.2 |
| 60 | B | G37 | crystal. | - | | 10 | 100 | 0.1 |
| 61 | B | G37 | sorpt. | n. comp. | | | | |
| 62 | E | G38 | crystal. | - | | 55 | 2 | 0 |
| 63 | E | G38 | sorpt. | - | | 25 | 94 | 0.2 |
| 64 | E | G39 | crystal. | + | | 45 | 82 | 0.4 |
| 65 | E | G39 | sorpt. | + | | 46 | 90 | 0.4 |
| 66 | D | G40 | crystal. | + | | 68 | 92 | 0.6 |
| 67 | D | G40 | sorpt. | n. comp. | | | | |
| 68 | A | G41 | sorpt.hexane | - | 2:1 | 85 | 95 | 0.8 |
| 69 | A | G41 | sorpt.$H_2O$ | - | 2:1 | 85 | 98 | 0.8 |
| 70 | A | G41 | fract.dist. | - | | 40 | 96 | 0.4 |
| 71 | A | G42 | sorpt. | - | 2:1 | 96 | 62 | 0.6 |
| 72 | A | G42 | sorpt.hexane | - | | 75 | 100 | 0.8 |
| 73 | A | G42 | sorpt.$H_2O$ | - | | 75 | 98 | 0.7 |
| 74 | A | G21 | fract.dist. | - | | 47 | 92 | 0.4 |
| 75-77 | A,D,E | G43 | sorpt. | n. comp. | | | | |
| 78-80 | A,D,E | G44 | sorpt. | n. comp. | | | | |
| 81 | A | G45 | sorpt. | - | 3:1 | 26 | 76 | 0.2 |

| entry | host | guest | method | product | host:guest | yield % | *e.e.* % | S |
|---|---|---|---|---|---|---|---|---|
| 82 | A | G45 | crystal. | n. comp. | | | | |
| 83 | D | G45 | sorpt. | - | 2:1 | 44 | 99 | 0.4 |
| 84 | D | G45 | crystal. | n. comp. | | | | |
| 85 | E | G45 | sorpt. | - | 1:1 | 92 | 88 | 0.8 |
| 86 | A | G46 | sorpt. | + | 1:1 | 88 | 99 | 0.9 |
| 87 | D | G46 | sorpt. | + | 1:1 | 86 | 96 | 0.8 |
| 88 | E | G46 | sorpt. | rac. | 1:1 | 78 | 0 | 0 |
| 89 | A | G47 | sorpt. | + | 1:1 | 82 | 47 | 0.4 |
| 90 | D | G47 | sorpt. | + | 1:1 | 80 | 77 | 0.6 |
| 91 | E | G47 | sorpt. | rac. | 1:1 | 90 | 0 | 0 |
| 92 | A | G48 | sorpt. | - | 2:1 | 76 | 93 | 0.7 |
| 93 | A | G49 | sorpt. | - | 2:1 | 84 | 86 | 0.7 |
| 94 | D | G50 | sorpt. | - | 1:1 | 61 | 97 | 0.6 |
| 95 | E | G50 | sorpt. | - | 1:1 | 56 | 97 | 0.5 |
| 96 | E | G50 | fract.dist. | - | | 55 | 98 | 0.5 |
| 97 | D | G50 | sorpt.hexane | - | | 82 | 100 | 0.8 |
| 98 | D | G50 | fract.dist. | - | | 60 | 93 | 0.6 |
| 99 | A | G50 | sorpt.$H_2O$ | - | | 73 | 100 | 0.7 |
| 100 | D | G51 | sorpt. | + | 1:1 | 38 | 100 | 0.4 |
| 101 | D | G51 | sorpt.hexane | + | | 78 | 75 | 0.6 |
| 102 | D | G51 | fract.dist. | + | | 60 | 94 | 0.6 |
| 103 | D | G52 | sorpt. | - | 2:1 | 63 | 63 | 0.4 |
| 104 | E | G53 | sorpt. | + | 1:1 | 82 | 57 | 0.5 |
| 105 | E | G54 | sorpt. | + | 1:1 | 75 | 98 | 0.7 |
| 106 | E | G55 | sorpt. | - | 1:1 | 70 | 96 | 0.7 |
| 107 | E | G56 | sorpt. | - | 3:2 | 55 | 49 | 0.3 |
| 108 | D | G57 | sorpt.hexane | + | | 93 | 78 | 0.7 |
| 109 | D | G58 | fract.dist. | + | | 39 | 92 | 0.4 |
| 110 | A | G58 | sorpt.hexane | + | | 89 | 92 | 0.8 |
| 111 | A | G58 | sorpt.$H_2O$ | + | | 76 | 100 | 0.8 |
| 112 | A | G58 | fract.dist. | + | | 17 | 96 | 0.2 |
| 113 | D | G59 | sorpt.hexane | + | | 80 | 80 | 0.6 |
| 114 | E | G59 | fract.dist. | + | | 30 | 94 | 0.3 |
| 115 | E | G60 | sorpt.hexane | + | | 76 | 75 | 0.6 |
| 116 | E | G60 | sorpt.$H_2O$ | + | | 74 | 47 | 0.3 |
| 117 | D | G61 | sorpt.hexane | + | | 75 | 100 | 0.8 |
| 118 | D | G61 | sorpt.$H_2O$ | + | | 89 | 100 | 0.9 |
| 119 | D | G61 | fract.dist. | + | | 74 | 92 | 0.7 |
| 120 | E | G61 | fract.dist. | + | | 78 | 90 | 0.7 |
| 121 | E | G62 | sorpt.hexane | + | | 78 | 100 | 0.8 |
| 122 | E | G62 | sorpt.$H_2O$ | + | | 80 | 100 | 0.8 |
| 123 | E | G62 | fract.dist. | + | | 58 | 92 | 0.5 |
| 124 | D | G63 | sorpt.hexane | + | | 59 | 70 | 0.4 |
| 125 | D | G63 | sorpt.$H_2O$ | + | | 52 | 86 | 0.4 |
| 126 | A | G64 | sorpt. | + | 2:1 | 70 | 61 | 0.4 |
| 127 | D | G64 | sorpt. | - | 1:1 | 29 | 82 | 0.2 |

| entry | host | guest | method | product | host:guest | yield % | *e.e.* % | S |
|---|---|---|---|---|---|---|---|---|
| 128 | E | G64 | sorpt. | + | 2:1 | 48 | 41 | 0.2 |
| 129 | A | G64 | crystal. | | | | | |
| 130 | D | G64 | crystal. | - | 1:1 | 47 | 79 | 0.4 |
| 131 | E | G64 | crystal. | - | 2:1 | 39 | 85 | 0.3 |
| 132 | A | G65 | sorpt. | + | 1:1 | 37 | 57 | 0.2 |
| 133 | D | G65 | sorpt. | + | 1:1 | 14 | 64 | 0.1 |
| 134 | E | G65 | sorpt. | + | 1:1 | 11 | 72 | 0.1 |
| 135 | A | G65 | crystal. | | | | | |
| 136 | D | G65 | crystal. | + | 1:1 | 18 | 73 | 0.1 |
| 137 | E | G65 | crystal. | + | 1:1 | 10 | 85 | 0.1 |
| 138 | A | G66 | sorpt. | - | 2:1 | 21 | 52 | 0.1 |
| 139 | D | G66 | sorpt. | + | 2:1 | 41 | 50 | 0.2 |
| 140 | E | G66 | sorpt. | + | 2:1 | 54 | 29 | 0.2 |
| 141 | A | G66 | crystal. | | | | | |
| 142 | D | G66 | crystal. | | | | | |
| 143 | E | G66 | crystal. | + | 2:1 | 43 | 16 | 0.1 |
| 144 | A | G67 | sorpt. | | | | | |
| 145 | D | G67 | sorpt. | + | 2:1 | 26 | 81 | 0.2 |
| 146 | E | G67 | sorpt. | + | 1:1 | 25 | 25 | 0.1 |
| 147 | A | G67 | crystal. | | | | | |
| 148 | D | G67 | crystal. | + | 2:1 | 28 | 29 | 0.1 |
| 149 | E | G67 | crystal. | + | 1:1 | 35 | 90 | 0.3 |
| 150 | D | G68 | sorpt. | - | 1:1 | 35 | 45 | 0.2 |
| 151 | D | G68 | crystal. | - | 1:1 | 23 | 42 | 0.1 |
| 152 | A | G69 | sorpt. | + | 1:1 | 20 | 24 | 0 |
| 153 | D | G69 | sorpt. | - | 1:1 | 33 | 48 | 0.2 |
| 154 | E | G69 | sorpt. | - | 1:1 | 53 | 64 | 0.3 |
| 155 | D | G69 | crystal. | - | 1:1 | 57 | 58 | 0.3 |
| 156 | E | G69 | crystal. | - | 1:1 | 41 | 64 | 0.3 |
| 157 | E | G70 | crystal. | *(S)-cis* | 1:1 | | | |
| 158 | E | G71 | crystal. | *S* | 1:1 | 30 | 99 | 0.3 |
| 159 | A | G72 | crystal. | *1R2R* | 1:1 | 52 | 100 | 0.5 |
| 160 | E | G73 | crystal. | - | 1:1 | 63 | 67 | 0.4 |
| 161 | E | G74 | crystal. | + | 1:1 | 28 | 100 | 0.3 |
| 162 | A | G75 | crystal. | + | 1:1 | 90 | 33 | 0.3 |
| 163 | E | G75 | crystal. | | 1:1 | 0 | 0 | 0 |
| 164 | D | G75 | crystal. | - | 1:1 | 16 | 100 | 0.2 |
| 165 | D | G75 | grind. | + | 1:1 | 83 | 34 | 0.3 |
| 166 | E | G76 | crystal. | + | 1:1 | 50 | 100 | 0.5 |
| 167 | E | G76 | grind. | + | 1:1 | 96 | 27 | 0.3 |
| 168 | E | G77 | crystal. | + | 1:1 | 38 | 100 | 0.4 |
| 169 | E | G78 | crystal. | + | 1:1 | 30 | 100 | 0.3 |
| 170 | E | G78 | grind. | + | 1:1 | 79 | 46 | 0.4 |
| 171 | A | G79 | crystal. | + | 1:1 | 26 | 100 | 0.3 |
| 172 | D | G79 | grind. | + | 1:1 | 75 | 54 | 0.4 |
| 173 | D | G79 | crystal. | + | 1:1 | 63 | 100 | 0.6 |

| entry | host | guest | method | product | host:guest | yield % | *e.e.* % | S |
|---|---|---|---|---|---|---|---|---|
| 174 | E | G80 | fract.dist. | - | | 98 | 100 | 1 |
| 175 | E | G80 | crystal. | - | 1:1 | | | |
| 176 | E | G81 | fract.dist. | - | | 10 | 90 | 0.1 |
| 177 | A | G82 | fract.dist. | - | | 39 | 90 | 0.4 |
| 178 | E | G83 | fract.dist. | - | | 18 | 95 | 0.2 |
| 179 | D | G84 | crystal. | + | 1:1 | 59 | 43 | 0.3 |
| 180 | D | G85 | crystal. | + | 1:1 | 56 | 100 | 0.6 |
| 181 | D | G86 | crystal. | + | 1:1 | 19 | 98 | 0.2 |
| 182 | D | G86 | grind. | + | 1:1 | 68 | 52 | 0.4 |
| 183 | D | G87 | crystal. | + | 1:1 | 40 | 98 | 0.4 |
| 184 | D | G87 | grind. | + | 1:1 | 64 | 50 | 0.3 |

S=k·t k = chemical yield, k=1 for 100% (one enantiomer present in racemic mixture)
t = optical purity, t=1 for 100% *e.e.*

**Table 2.3:** Inclusion resolutions performed by Toda and co-workers[1-11,15,18,20-28,31-45,50,61]

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# 3 Inclusion experiments with Taddol hosts

*In this chapter the inclusion capabilities of newly designed and already known Taddols are described. A wide variety of racemic compounds such as alcohols, organic acids, amines, nitriles and ketones has been used. The Taddols have been applied individually as well as in mixtures in several inclusion resolution experiments using various techniques.*

## 3.1 Introduction

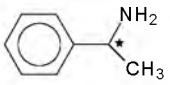
As was described in chapter 2, Taddols are very suitable compounds for the enantioselective preparation of inclusion complexes. Toda[20-45,47] and others[14-19] extensively studied a limited number of Taddols, and in these experiments the Taddols showed a great potential as practical tool for the resolution of neutral, chiral molecules.
The readily accessibility of a variety of new Taddols, which have not been studied in inclusion complexation before, inspired a further exploration of capabilities and limitations of these compounds as resolving agents. Information about the suitability of inclusion resolution for application in industry will so be collected.
The previous chapter focussed on the syntheses of a variety of known and new Taddols. In this chapter, the attempts to prepare inclusion complexes with twelve different Taddols as potential host molecules and a large selection of guest compounds using different techniques are described. These potential guest compounds were selected from a variety of classes including alcohols, amines, esters, nitriles and acids.
The Taddols in this study have not only been applied as single, individual resolving agents, but also as mixtures. In the resolution *via* diastereomeric salts, mixtures of structurally related resolving agents improved the racemate separation (Dutch Resolution[54]). The influence of mixtures on nucleation and selectivity of an inclusion resolution process was therefore studied.
Finally, the use of high pressure, which might influence enantioselectivity and induce nucleation of the inclusion complex, was investigated.

## 3.2 Guest compounds

The guest compounds known to be included in Taddol host compounds should fulfil certain criteria, as can be learned from an analysis of the literature examples (see appendix of chapter 2). All guests described so far are relatively small compounds and most contain functional groups, suitable for hydrogen bonding with the Taddols, e.g. amino, alcohol, *etc.*.
Moreover, the guest molecules have been selected, as far as possible, with respect to their industrial relevance. Many of them are precursors for pharmaceuticals or other fine chemicals. These criteria have played a major role in the selection of the guest used in the present research.
Since the resolution of larger molecules is also desirable in industry, the selection of guests additionally contains some larger sized guest molecules.
The majority of guest compounds are readily available as racemates and many have been proven to be difficult to resolve. Some could be racemised under mild conditions and are therefore possible candidates for the application of asymmetric transformation.

Figure 3.1 gives an overview of all guest compounds used, divided into different categories.

**Amines**

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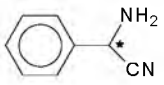


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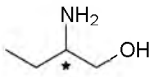


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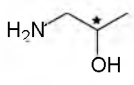


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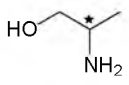


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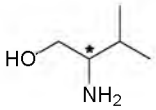


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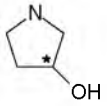
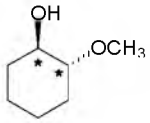



**R7**

**Alcohols**

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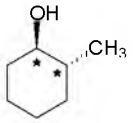


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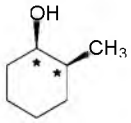


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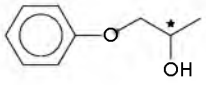


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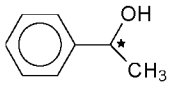


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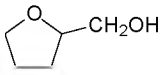


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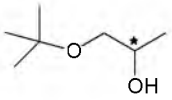


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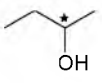


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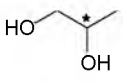


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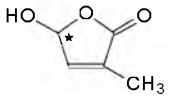


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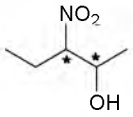


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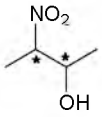


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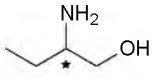


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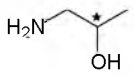


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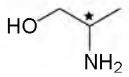


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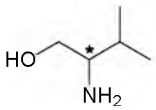


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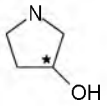


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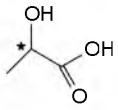


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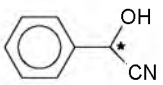


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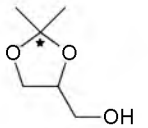


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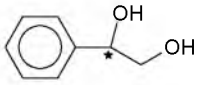


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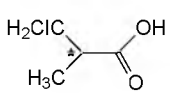


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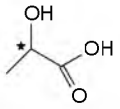


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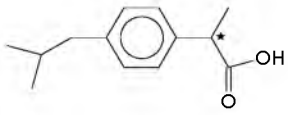


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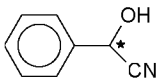


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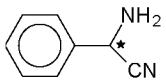
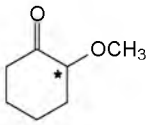


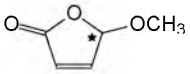

**R2**


**R21**

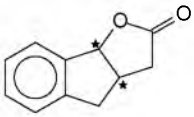
**Miscellaneous**




**R27**




**R28**




**R29**


**R30**

**Figure 3.1:** 30 racemic guest compounds

The racemic guest compounds are classified according to their functional groups; a few are therefore mentioned twice.

## 3.3 Inclusion experiments

As described in chapter 2, a number of different methods to prepare inclusion complexes are known. The initial, most frequently applied method in this research project is also the most common one: crystallisation occurring from solution with an appropriate solvent. Furthermore, selected experiments were performed with the solvent-free crystallisation technique, vapour sorption and grinding.
Before describing the inclusion experiments, the term nucleation will be explained, since it plays an essential role in inclusion complexation.

### 3.3.1 Nucleation[9-13]

The term "crystallisation" stands for a description of two combined processes, namely nucleation and crystal growth. Nucleation refers to the creation of a nucleus on which, subsequently, a crystal will grow to a detectable size. If there is a lack of nuclei, no crystal will grow at all.

In order for either of these processes to occur, the system must be supersaturated. This means that the concentration of solute exceeds the saturated value in solution at a given temperature and pressure. Thermodynamically, a supersaturated solution is a non-equilibrium (metastable) state. While turning into a thermodynamically stable state, the saturated binary solution will phase-separate into two different phases, a solute-rich and a solute-poor one. As result of fluctuations, small quantities of the solute-rich phase (the nuclei) are formed in the original metastable phase. These nuclei are unstable and may dissolve immediately again. If they are large enough to compensate the unfavourable energy change, which occurs at the interface between both phases, the solute-rich and the solute-poor, they are beyond their critical size and crystal growth will occur.

The thermodynamic laws require a smaller free energy of the crystalline phase than for that phase, from which the crystal is forming. Taking the free energy change associated with precipitation into consideration, it is usually assumed that each particle that becomes part of the crystal undergoes the same change in energy. However, this is not exactly true. Those particles present in the interior of the solid have a certain energy, the so-called solid-energy. The small number of particles present at the surface of the solid has a higher energy and is therefore less stable, because they do not have the same co-ordination as those in the interior of the solid. In this way, an additional surface contribution to the overall energy of the precipitate is represented.

The total energy of a phase ($G_{tot.}$) can be defined by the sum of the surface energy per unit volume ($G_s$) and the volume components ($G_v$). For a spherical crystal, the surface contribution will always be proportional to $4r^2$, whereas the volume contribution will always be proportional to $4/3r^3$. The total energy of a system can thus be represented by the following equation:

$$G_{tot.} = G_s 4r^2 - G_v 4/3r^3 \qquad \textbf{Equation 3.1}$$

The significance of this equation is illustrated in Figure 3.2. After a crystal has reached a certain size, given by the critical growth radius ($r_c$), crystal growth will proceed spontaneously since it results in lower energy ($\Delta G<0$). However, for smaller crystals where $r<r_C$, the first term in the equation dominates the total energy change ($\Delta G>0$). These crystals are unstable and likely to dissolve again. This effect is called nucleation barrier. This barrier must be overcome to induce crystallisation, this means that a nucleus where $r>r_C$ must be obtained. This can be achieved by two methods. Due to the Boltzman distribution, nuclei of a certain size always have a certain chance of occurring, meaning that a nucleus of adequate size will always be formed given enough time. However, at low supersaturation especially, the time required may be unacceptably long. Increasing the degree of supersaturation can therefore enhance the chance of obtaining a sufficient-sized nucleus. This will be accompanied by the possible effect of the nucleation barrier.

As spontaneous nucleation depends on chance, it should be noted that the experimental scale is an important factor; the more material, the greater the chance of spontaneous nucleation.

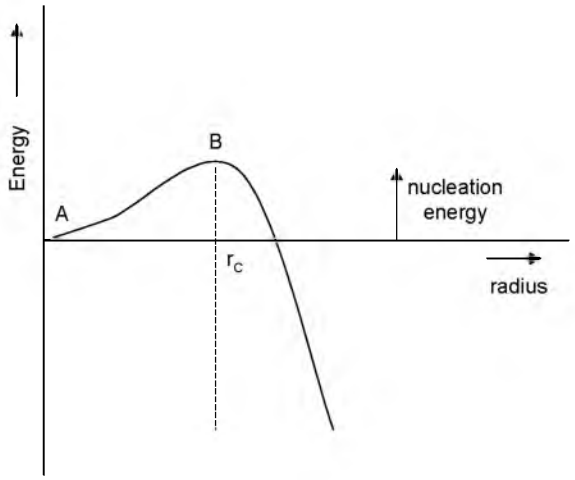



**Figure 3.2:** Crystal growth

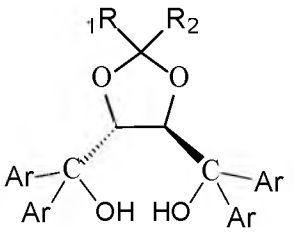
The use of another solvent, or seeding the solution, can induce crystal growth. The obvious problem is, that because of the lack of crystalline material of the special compound, no suitable seeds may be available. Sometimes foreign material will have a similar effect, in case it has a high affinity to, or is of analogous crystalline structure as the compound to be crystallised.

If a compound has strong interactions in the solid state, its nucleation barrier will usually be lower compared to that of less tightly bonded crystals.

Comparing diastereomeric salts with inclusion complexes it is very likely that salts, with their strong electrostatic interactions and hydrogen bridges, will nucleate more easily than the uncharged and often only weakly bonded inclusion complexes. In inclusion crystallisation, the change from an irregular mixed state of two compounds to a regular state, resulting in a more unfavourable change in entropy than in the crystallisation of a single, pure compound, constitutes another important reason for difficulties in obtaining crystals.

### 3.3.2 Crystallisation experiments with solvent

In order to form inclusion complexes with different guests, the pure Taddols have been dissolved together with the respective guest compound in hexane/toluene (1:1) or heptane. The experiments were executed with a host/guest ratio of 1:1 at room temperature. In Table 3.1 the results are collected.




$R_1,R_2$ = -methyl
Ar = -phenyl **1**
-*o*-tolyl **2**
-*m*-tolyl **3**
-*p*-tolyl **4**
-*o*-anisyl **5**
-*m*-anisyl **6**
-*p*-anisyl **7**
-*p*-Cl-phenyl **8**

$R_1,R_2$ = -cyclohexyl
Ar = -phenyl **9**
-*p*-tolyl **10**

Ar = -*p*-tolyl
$R_1,R_2$ = -H **11**
$R_1$ = -H, $R_2$ = -phenyl **12**

| racemic guests | | host compounds | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
| R1 | phenylethylamine (PEA) | x* | O | O | 1:1 | x | O | x | O | O | x | x | x |
| R2 | 2-phenylglycinonitrile | x | x | O | O | x | O | x | O | O | O | x | O |
| R3 | 2-amino-1-butanol | O | O | O | O | x | O | O | x | 1:2 | O | x | O |
| R4 | 1-amino-2-propanol | x | x | O | O | x | O | x | O | 1:2 | 2:3 | x | x |
| R5 | 2-amino-1-propanol | 1:1 | x | x | 1:1 | O | O | 1:1 | x | 1:1* | x | 1:2 | O |
| R6 | 2-amino-3-methyl-1-butanol | O | 1:1 | O | x | x | O | O | x | 1:1 | O | 1:1 | O |
| R7 | pyrrolidinol | 1:1 | x | O | 1:1 | x | O | 1:2 | x | 1:1 | x | O | x |
| R8 | *trans*-2-methoxycyclohexanol | x | x | O | 2:1 | x | O | O | O | x | 1:1 | O | x |
| R9 | *trans*-2-methylcyclohexanol | x | x | 2:1 | x | x | O | O | O | O | 1:1 | x | O |
| R10 | *cis*-2-methylcyclohexanol | x | O | O | 1:1 | x | O | x | O | O | O | x | O |
| R11 | 1-phenoxy-2-propanol | x | O | x | O | O | O | O | O | O | O | O | x |
| R12 | phenethylalcohol | x | O | O | O | x | O | O | x | x | O | x | O |
| R13 | tetrahydrofurfuryl alcohol | x* | x | x | O | O | O | x | O | O | O | O | O |
| R14 | 1-*tert*-butoxy-2-propanol | x | x | x | O | O | O | O | O | O | x | O | x |
| R15 | *sec*-butanol | x | x | O | O | x | O | O | O | x | x | x | O |
| R16 | 1,2-propandiol | 1:1 | x | O | 1:2 | O | O | 1:2 | O | 1:1 | O | 1:1 | O |
| R17 | 5-hydroxy-3-methyl-2,5-dihydro-2-furanone | x | x | x | x | x | x | x | O | x | x | x | O |
| R18 | 3-nitro-2-pentanol | x | x | O | x | O | O | x | O | 1:2 | 1:1 | x | O |
| R19 | 3-nitro-2-butanol | x | O | O | x | x | O | x | O | x | x | x | O |
| R20 | lactic acid | x | 2:1 | O | x | O | O | O | O | x | 2:1 | 1:1 | O |
| R21 | lactonitrile | x | 3:2 | O | 1:1 | x | O | x | x | x | O | x | O |
| R22 | mandelonitrile | O | x | O | O | O | O | O | x | x | O | x | x |
| R23 | solketal | O | 2:1 | O | x | 2:1 | O | x | O | x | x | x | O |
| R24 | 1-phenyl-1,2-ethanediol | x | O | O | x | O | O | O | x | x | x | x | x |
| R25 | $\beta$-chloro-*iso*-butyric acid | x | x | 2:1 | 1:1 | x | O | O | O | O | O | x | O |
| R26 | ibuprofen | x | x | x | x | x | O | x | O | x | x | x | O |
| R27 | 2-methoxycyclohexanone | x | x | O | 1:1 | x | O | x | O | x | x | x | O |
| R28 | 5-methoxy-5*H*-furan-2-one | x | x | O | x | x | O | x | O | x* | x | x | O |
| R29 | 3,3a,4,8b-tetrahydro-2*H*-indeno[1,2b]-furan-2-one | x | x | x | x | x | O | x | O | x | x | x | O |
| R30 | propylene oxide | x | O | O | O | x | O | x | O | x* | x | x | O |

x = crystals of pure Taddol
O = gels
x:x = host/guest ratio of inclusion complex
* = resolution already described in literature

**Table 3.1:** 360 inclusion crystallisation experiments with solvent

The formation of inclusion complexes requires a higher stability and lower solubility of these complexes compared to the individual components. Obviously, these conditions will not be fulfilled in all attempted cases. However, in many experiments shown in Table 3.1, obtaining the first crystalline material (nucleation) might limit the rate of success. In a discussion with Professor Toda he admitted to having similar problems in obtaining the first batch of crystals. The existence of strong interactions between host and guest is, in many cases, indicated by the formation of gels. Attempts to disrupt the gels and induce crystallisation by the application of ultrasound met with no success. Disrupting the gels by mechanically stirring was impossible due to the small scale of the experiments. However, once frozen in a gel matrix, the possibility of crystallisation is considerably reduced.

In 45% of all experiments the pure host crystallised, without the inclusion of any compound (proven by $^{1}$H-NMR).
Five attempts to repeat resolutions described by Toda, led only in one case to the described inclusion complex. In the other four batches, pure crystals of the respective Taddols were obtained. Probably nucleation problems are the reason for this failure.
Fortunately, in 38 cases inclusion complexes have been obtained, including the successful reproduction of a resolution described by Toda. The results are summarised in Table 3.2.

| entry | host/guest | chirality guest | e.e./ method | yield | S | recovery method |
|---|---|---|---|---|---|---|
| 1 | **1**/R5 (1:1) | | 0 / A | 42% | 0 | M |
| 2 | **1**/R7 (1:1) | | 0 / C | 33% | 0 | M |
| 3 | **1**/R16 (1:1) | | 0/ B | 12% | 0 | M |
| 4 | **2**/R6 (1:1) | | 0/ B | 8% | 0 | M |
| 5 | **2**/R20 (2:1) | (*S*) | 71% / I | 11% | 0.1 | M |
| 6 | **2**/R21 (3:2) | | 0 / B | 22% | 0 | M |
| 7 | **2**/R23 (2:1) | | 0 / G | 19% | 0 | M |
| 8 | **3**/R9 (2:1) | | 0 / B | 23% | 0 | K |
| 9 | **3**/R25 (2:1) | | 0 / B | 17% | 0 | K |
| 10 | **4**/R1 (1:1) | L | 95% / A | 41% | 0.8 | M |
| 11 | **4**/R5 (1:1) | | 0 / A | 13% | 0 | M |
| 12 | **4**/R7 (1:1) | | 0 / C | 13% | 0 | M |
| 13 | **4**/R8 (2:1) | (*S,S*) | 94% / D | 39% | 0.8 | M |
| 14 | **4**/R10 (1:1) | | 0 / B | 18% | 0 | M |
| 15 | **4**/R16 (1:2) | | 0 / B | 9% | 0 | M |
| 16 | **4**/R21 (1:1) | | 0 / B | 18% | 0 | M |
| 17 | **4**/R25 (1:1) | | 0 / B | 22% | 0 | M |
| 18 | **4**/R27 (1:1) | | 0 / B | 23% | 0 | M |
| 19 | **5**/R23 (2:1) | | 0 / G | 19% | 0 | K |

| entry | host/guest | chirality guest | e.e./ method | yield | S | recovery method |
|---|---|---|---|---|---|---|
| 20 | **7**/R5 (1:1) | | 0 / A | 9% | 0 | K |
| 21 | **7**/R7 (1:2) | | 0 / C | 31% | 0 | K |
| 22 | **7**/R16 (1:2) | | 0 / B | 22% | 0 | K |
| 23 | **9**/R3 (1:2) | | 0 / A | 22% | 0 | M |
| 24 | **9**/R4 (1:2) | | 0 / A | 24% | 0 | M |
| 25 | **9**/R5 (1:1) | not determined | 21% / A | 24% | 0.1 | M |
| 26 | **9**/R6 (1:1) | | 0 / B | 5% | 0 | M |
| 27 | **9**/R7 (1:1) | | 0 / C | 11% | 0 | M |
| 28 | **9**/R16 (1:1) | | 0 / B | 19% | 0 | M |
| 29* | **9**/R18 (1:2) | | 0 / G | 22% | 0 | M |
| 30 | **10**/R4 (2:3) | | 0 / A | 21% | 0 | K |
| 31 | **10**/R8 (1:1) | | 0 / D | 34% | 0 | K |
| 32 | **10**/R9 (1:1) | | 0 / B | 25% | 0 | K |
| 33 | **10**/R18 (1:1) | | 0 / G | 27% | 0 | K |
| 34 | **10**/R20 (2:1) | (*S*) | 66% / I | 19% | 0.2 | M |
| 35 | **11**/R5 (1:2) | | 0 / A | 33% | 0 | K |
| 36 | **11**/R6 (1:1) | | 0 / B | 24% | 0 | K |
| 37 | **11**/R16 (1:1) | | 0 / B | 27% | 0 | K |
| 38 | **11**/R20 (1:1) | | 0 / I | 37% | 0 | K |

* resolution described in literature
M inclusion crystallisation with MeOH
A-I see Table 3.3
K bulb-to-bulb distillation

**Table 3.2:** Successful inclusion experiments

All host/guest ratios have been determined by $^{1}$H-NMR spectroscopy.

The guest compounds were isolated from the respective inclusion complexes by two different methods; dissolving in methanol followed by crystallisation of the more stable host-methanol complex or bulb-to-bulb distillation. The latter crude distillation technique cannot completely avoid the co-distillation of some host compound. However, since only small amounts of crystalline inclusion material (0.1g-0.5g) were available, this method was most suitable for separation of many inclusion complexes. In the alternative method, the inclusion complex was dissolved in methanol, which can also be included into the Taddols. As a competitor, more stable methanol inclusion crystals precipitated and the released guest compound was isolated from the filtrate. Hence, small amounts of the Taddols may stay in solution and contaminate the product.

The hosts that have been recovered in both methods, however, are pure enough to be used again in resolution experiments. Since the isolated guest compounds still contain small

impurities derived from the respective hosts, the *e.e.*'s determined with optical rotation (method B) should be treated with care.
The development of methods to determine the *e.e.*'s is very time-consuming. As described above, the determination of the optical rotation is not completely reliable, therefore alternative *e.e.* determination techniques have been developed for many of the racemates.
The methods developed and applied are collected in the following table (Table 3.3).

| *e.e.* determination method | | can be applied to |
|---|---|---|
| A | derivative, camphonyl chloride, GC, β-CD | R1,R3-5 |
| B | optical rotation | R2,R6,R9-10,R15-R17,R21-R23,R25-R30 |
| C | derivative, benzoyl chloride, HPLC, OD-H | R7,R11 |
| D | derivative, camphonyl chloride, $^1$H-NMR | R8 |
| E | HPLC, OD-H | R12 |
| F | derivative, benzoyl chloride, HPLC, OB | R13 |
| G | GC, β-CD | R14,R18 |
| H | derivative, benzoyl chloride, GC, β-CD | R19 |
| I | derivative, diazomethane, GC, β-CD | R20 |
| J | HPLC, OB | R24 |

**Table 3.3:** Methods developed to determine the *e.e.*

Only in five cases of all inclusion complexes obtained was resolution observed, the other inclusion complexes only contained the racemic guest compounds. Two of the inclusion complexes, entries 10 and 13, afforded high efficiencies (0.8) after a single re-crystallisation. In both of these experiments Taddol **4** was used as resolving agent. In general, Taddol **4** has proven to be a suitable host compound.

### 3.3.3 X-ray structure analyses of inclusion complexes

Three of the new inclusion complexes were found to be suitable for analysis by X-ray. A literature survey[20-45] revealed that the Taddols tend to show characteristic behaviour in binding to their included guest molecules, independent of the final complex structure. Depending on the respective guest compound, the Taddols can form cavities, channels or layers, in which the guest molecule is included. In the cavities, one or more guest molecules are arranged isolated from each other, whereas the layer structure accommodates the guest molecules in linked chains. In the third type, host and guest together form a sandwich structure, arranged in different layers.
In the 1:1 inclusion inclusion complex of Taddol **4** and L-phenylethylamine (R1) (entry 10), the two hydroxy-groups of the Taddol molecule are hydrogen-bonded to each other, leaving one hydroxy-hydrogen in a free position to form a hydrogen bond to the guest molecule. The two aromatic groups of each diarylcarbinol part are oriented perpendicular to each other.

The X-ray structures of this inclusion compound and a segment showing only the host compound are depicted in Figure 3.3 and Figure 3.4.

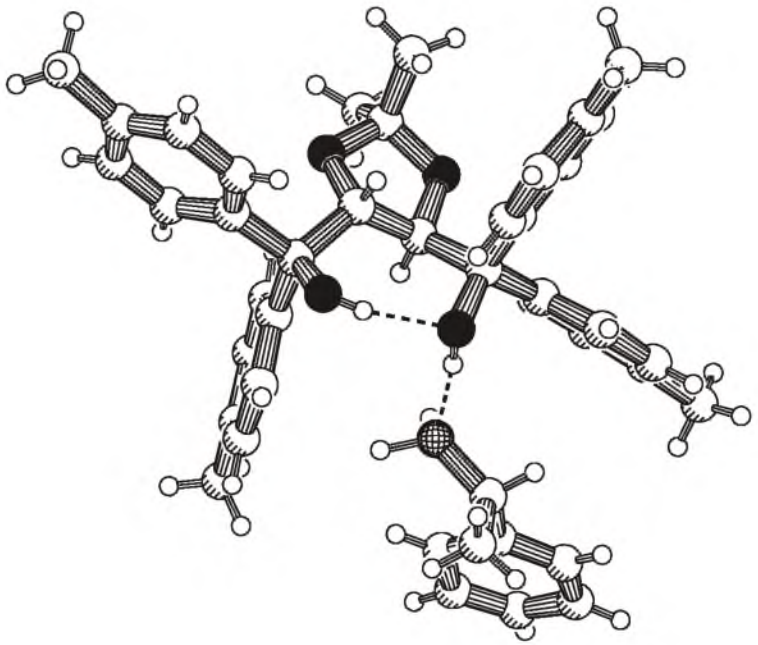


**Figure 3.3:** A PLUTON drawing of the 1:1 inclusion complex of Taddol **4** and L-phenylethylamine (R1) (entry 10)

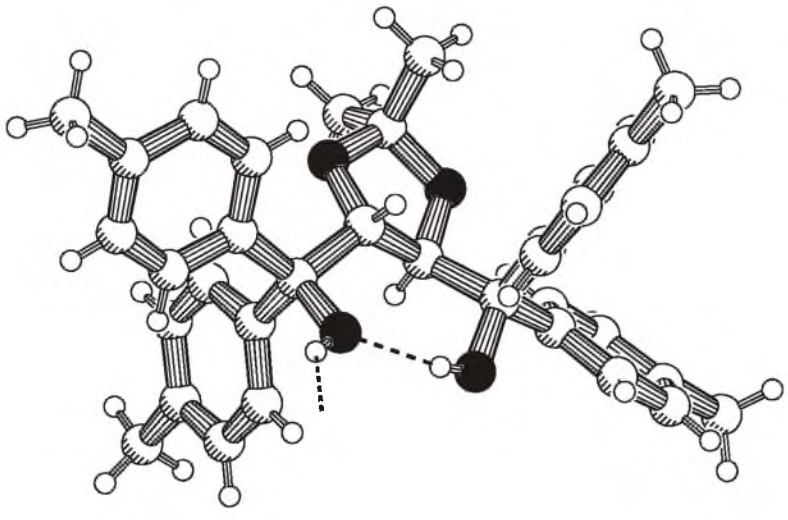


**Figure 3.4:** A PLUTON drawing of the host segment of the 1:1 inclusion complex of Taddol **4** and L-phenylethylamine (R1) (entry 10)

In the 2:1 inclusion inclusion complex of Taddol **4** and (*S,S*)-*trans*-2-methoxycyclohexanol (R8) (entry 13), the two hydroxy-groups of both Taddol molecules are internally hydrogen-bonded to each other, leaving one hydroxy-hydrogen in a free position to form a hydrogen bond to the guest molecule or to the other Taddol molecule. In this inclusion complex both Taddols form a dimer, which is then hydrogen-bonded to the guest. The X-ray structure of this inclusion compound is depicted in Figure 3.5.

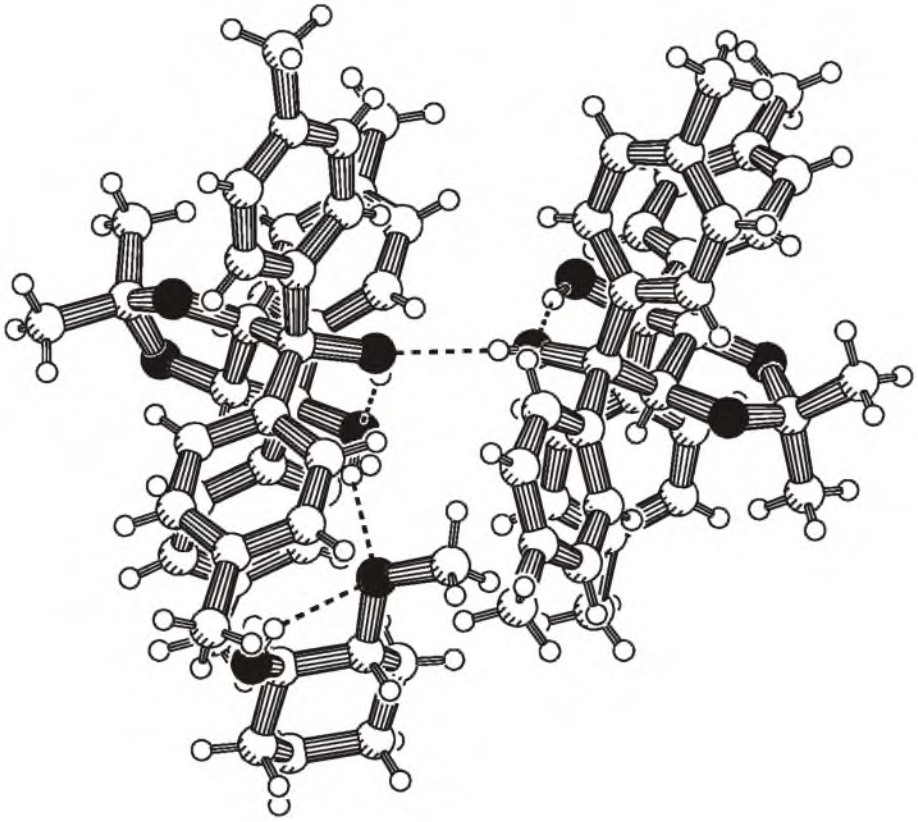


**Figure 3.5:** A PLUTON drawing of the inclusion complex of Taddol **4** and *(S,S)-trans*-2-methoxycyclohexanol (R8) (entry 13)

In the 2:1 inclusion inclusion complex of Taddol **10** and *(S)*-lactic acid (R20) (entry 34), the two hydroxy-groups of both Taddol molecules are again internally hydrogen-bonded to each other, leaving one hydroxy-hydrogen in a free position to form a hydrogen-bond to the guest molecule. In this inclusion complex the two Taddols do not form a dimer, but the guest molecule is hydrogen-bonded to one Taddol with its alcohol function and with its acid function to the other Taddol molecule. Additionally, the guest forms an internal hydrogen-bond.

The X-ray structure of this inclusion compound is depicted in Figure 3.6.

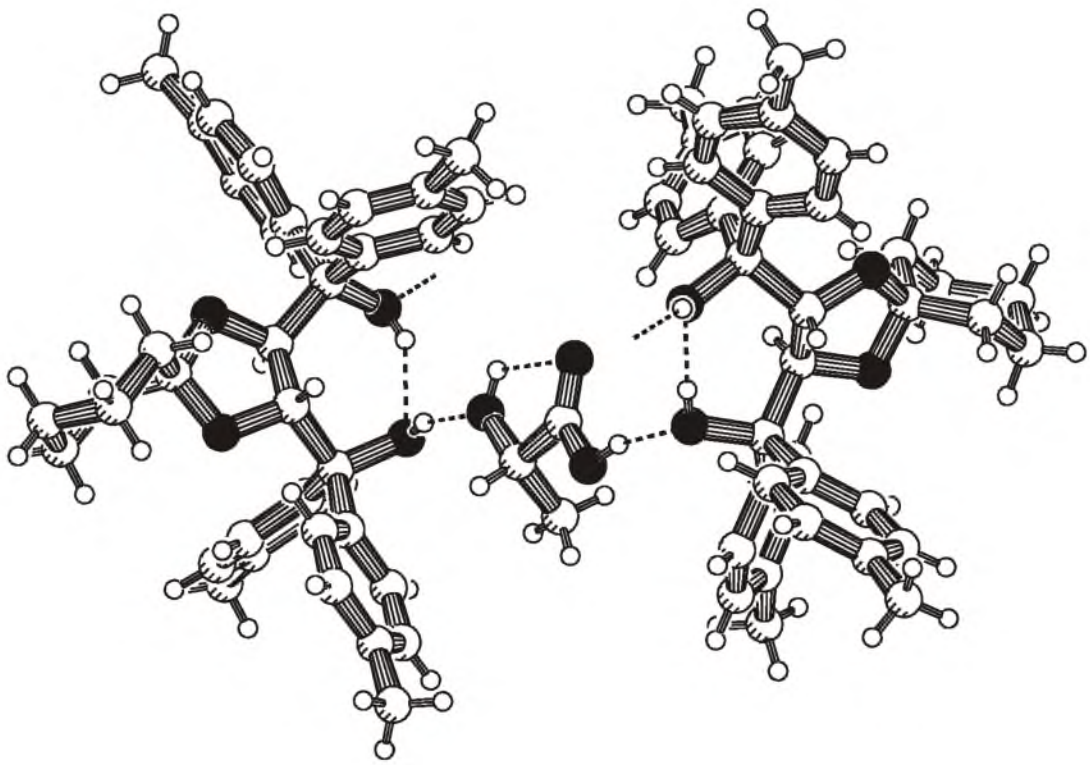


**Figure 3.6:** A PLUTON drawing of the inclusion complex of Taddol **10** and *(S)*- lactic acid (R20) (entry 34)

### 3.3.4 Crystallisation experiments under high pressure[4-8]

As described in paragraph 3.3.1, obtaining the first crystalline material in inclusion resolution can be difficult. In section 3.3.2 a large number of inclusion experiments is described which do not lead to inclusion complexes. This may be attributed to difficulties in overcoming the critical nucleation radius. As mentioned previously, influencing the nucleation barrier by changing the surface energy ($G_S$) by using different solvents is possible. Similarly, a change in the stability (energy) of the bulk of the crystal ($G_r$) will also lead to a change of the barrier. Having a closed system and performing only volume work at a constant temperature, the relationship between Gibbs free energy and pressure can be expressed as follows:

$dG = Vdp$ (V = volume, p = pressure) **Equation 3.2**

In order to calculate Gibbs free energy starting from a defined pressure ($p_A$) at a certain pressure ($p_E$), this gives:

$$G(p_E) = G(p_A) + \int_{p_A}^{p_E} Vdp$$ **Equation 3.3***

The relationship between pressure and free energy is dependant on the volume. As the process of crystallisation is accompanied by a change in volume (solids have the lowest volumes), the use of high pressure will have a strong influence on the solubility. At a higher pressure, crystallisation may therefore start more easily than at ambient pressure.

All attempts of forming inclusion crystals with Taddols **1** and **4** and the respective guest compounds which did not crystallise at normal pressure, have been repeated using 15 kbar of pressure for five hours. The experiments are listed in Table 3.4.

| Taddol | racemate |
|---|---|
| **1** | R3,R22,R23 |
| **4** | R2-R4,R6,R11-R15,R22,R23,R27,R30 |

**Table 3.4:** Inclusion crystallisation experiments performed at 15 kbar

In the majority of attempts to obtain inclusion crystals under high pressure, neither inclusion crystals nor pure host crystals were obtained. Only inclusion crystals of Taddol **4** and 2-methoxycyclohexanone were obtained, constituting a successful exception. Using these crystals as seeding material, inclusion crystals have also been obtained at ambient pressure (see Table 3.1).
Apparently, the application of high pressure can indeed be an auxiliary to obtain the first batch of crystals. High pressure can also influence the quality of a resolution process, as a literature search[1,2] has shown. If the two diastereomeric forms of an inclusion complex have different compressibilities, high pressure will influence the differences in solubilities between the two diastereomers.
Some experiments with phenylethylamine (PEA) and Taddol **4** have been executed in order to determine the influence of pressure on this resolution (see Table 3.5).

| molar ratio **4**/*rac.* PEA | 0 kbar *e.e.* *L*-PEA | 3 kbar *e.e.* L-PEA | 6 kbar *e.e.* L-PEA | 12 kbar *e.e.* L-PEA | 15 kbar *e.e.* L-PEA |
|---|---|---|---|---|---|
| 1:2 | 62 % | 59 % | 59 % | 59 % | 59 % |
| 1:4 | 68 % | 53 % | 42 % | 42 % | 42% |
| 1:20 | 66 % | 63 % | 57 % | 55% | 55%. |

**Table 3.5:** Resolution of phenylethylamine under pressure

* $dG = dH - TdS - SdT \wedge dH = dU + pdV + Vdp \Rightarrow dG = dU + pdV + Vdp - TdS - SdT$
with $dU = TdS - pdV \Rightarrow dG = TdS - pdV + pdV + Vdp - TdS - SdT = Vdp - SdT$
T const. $\Rightarrow dG = Vdp$

These experiments show the influence of pressure on the enantioselectivity. Initially, the *e.e.* obtained after a single crystallisation decreases under higher pressure, but this effect levels off quickly. A further increase of pressure no longer influences the quality of resolution. However, the application of high pressure has a negative impact on this resolution, leading to a decrease in the differences between the diastereomers and consequently a lower *e.e.*. Despite the negative effect on this resolution, it is conceivable that a positive effect may be obtained in other cases. As is generally the case with the effect of high pressure on nucleation, further studies will be required in the investigation of its influence on enantioselectivity.

### 3.3.5 Crystallisation experiments without additional solvent

Many inclusion experiments did not lead to inclusion crystals. This lack of success may be influenced by the crystallisation method applied. Literature examples (see appendix in chapter 2) have shown that in some cases inclusion complexes can only be obtained at very high concentrations at supersaturation and thus, the chances of nucleation are maximal. This can be achieved by dissolving the host compound in the guest compound without the use of a solvent.

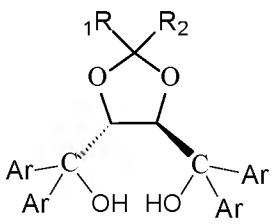
Several experiments have therefore been repeated using the solvent-free crystallisation technique, with the aim to increase the chance of nucleation and thus the number of successful inclusion experiments.

The Taddols **1**,**4**, **9** and **10** are the most effective hosts used, and in order to limit the number of additional experiments, they were selected for this series. The four potential hosts were dissolved in those liquid racemic guest compounds, which previously could not be included by crystallisation from a solvent.

Surprisingly, no new inclusion complexes were obtained using the solvent-free crystallisation technique. In most of the experiments only the pure host compound has crystallised, as was proven by $^{1}$H-NMR analyses.

Similar to the results from experiments with a solvent, gels were obtained in many cases.

To investigate whether a successfully formed inclusion complex derived from the crystallisation experiments in a solvent can be repeated with the solvent-free technique, the combination of Taddol **4** and phenylethylamine was tested. Taddol **4** indeed forms an inclusion complex with phenylethylamine *via* both crystallisation methods. Furthermore, the *e.e.* obtained after a single crystallisation increased from 72% to 79% working in a solvent-free environment.



$R_1$,$R_2$ = -methyl
Ar = -phenyl **1**
-*p*-tolyl **4**

$R_1$,$R_2$ = -cyclohexyl
Ar = -phenyl **9**
-*p*-tolyl **10**

| racemic guests | | host compound | | | |
|---|---|---|---|---|---|
| | | **1** | **4** | **9** | **10** |
| R1 | phenylethylamine (PEA) | x | — | O* | O |
| R3 | 2-amino-1-butanol | x | x | — | O* |
| R4 | 1-amino-2-propanol | x | x | — | — |
| R6 | 2-amino-3-methyl-1-butanol | x | x | — | O* |
| R8 | *trans*-2-methoxycyclohexanol | x | — | x | — |
| R9 | *trans*-2-methylcyclohexanol | x | x | x | — |
| R10 | *cis*-2-methylcyclohexanol | x | — | x | x |
| R11 | 1-phenoxy-2-propanol | x | x | x | x |
| R12 | phenethylalcohol | O | x | x | x |
| R13 | tetrahydrofurfuryl alcohol | x | x | x | x |
| R14 | 1-*tert* butoxy-2-propanol | x | x | x | x |
| R15 | *sec*-butanol | x | x | x | x |
| R18 | 3-nitro-2-pentanol | O | O | — | — |
| R19 | 3-nitro-2-butanol | O | O | x | — |
| R20 | lactic acid | O | — | O | — |
| R21 | lactonitrile | O | — | O | x |
| R25 | $\beta$-chloro-iso-butvric acid | O | — | O* | x |
| R27 | 2-methoxycyclohexanone | x | — | x | x |
| R28 | 5-methoxy-5*H*-furan-2-one | x | x | x | x |
| R30 | propylene oxide | O | x | x | O |

O gels — not performed
x pure host compound crystallised *also gel with solvent experiment

**Table 3.6:** 80 inclusion crystallisation experiments without solvent

### 3.3.6 Vapour sorption experiments

In the vapour sorption method, the gaseous guest compound is passed over the solid host compound and absorbed into the host crystal lattice. The host can also partially dissolve on its surface in the condensed guest compound, resulting in the formation of a combined crystal lattice, different to that of the pure host.

Since Taddol **4** is able to resolve phenylethylamine with an *e.e.* of 72% (95% after re-crystallisation) and can include both enantiomers separately leading to two diastereomeric crystals, this system was chosen to study the efficiency of the vapour sorption technique.

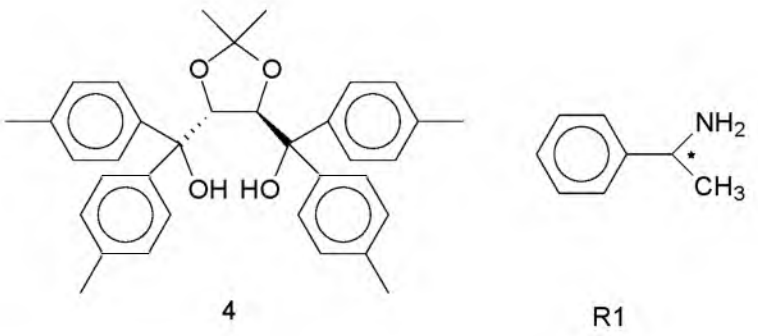



**Figure 3.7:** *(R,R)*-Taddol **4** and racemic phenylethylamine R1

The two diastereomeric inclusion crystals differ in their thermal behaviour. The D-amine inclusion complex decomposes at 103°C, at which temperature the amine evaporates, leaving the molten host behind, whereas the decomposition point of the L-included compound is 143°C. The experiment was performed at 110°C, a temperature between the melting points of the two diastereomers. Since the D-amine diastereomer should not be formed at all at this temperature, but the L- amine complex can, an increase of the resolution quality was expected.

However, the result did not meet expectations. Resolution and inclusion of the amine was observed, but the *e.e.* of the L-amine included was only 70%, approximately the same value as after a single crystallisation.

Thus, no improvement of the resolution of phenylethylamine with Taddol **4** has been achieved by the vapour sorption technique. Assuming that the inclusion complex formed is a solid solution in the amine component, with an optimal stability of the inclusion complex at the ratio$_{D/L}$ of 85:15 (= 70% *e.e.*), this effect is easily explainable.

Since the experiment did not increase the result of resolution, no further attempts have been performed using the vapour sorption method.

### 3.3.7 Grinding experiments

Using the grinding technique, host and guest are mixed and while grinding in a mortar, an inclusion complex will be formed.

Again, the system of Taddol **4** and phenylethylamine has been chosen to investigate the efficiency of this technique.

Solid host and liquid guest were combined in a ratio of 1:1 and 1:2 and ground in a mortar for 20 minutes. The solid was then washed with heptane and analysed. In both cases inclusion complexes were formed, however, the amine was included affording an *e.e.* of approximately only 50%, lower than in the application of the other methods.

Since this method does not offer any advantages, further investigations were not performed.

### 3.3.8 $^1$H-NMR shift experiments

With the exception of Taddols with different substituents in the acetonide moiety ($R_1 \neq R_2$), all Taddols have $C_2$-symmetry and show a singlet for the C4-H and C5-H protons in NMR.

An intramolecular hydrogen bond between the two hydroxy groups leaves one proton of the other hydroxy group available for intermolecular hydrogen donation. This allows good hydrogen-bond acceptors to be accommodated in the area of the hydroxy groups of the Taddol and thereby close to the aromatic part of the molecule. The shielding or de-shielding ring-current effect of Taddols aromatic moieties consequently influences the acceptor molecule. This results in different shifts for the protons of the two diastereomeric hydrogen-bonded complexes, which might then be distinguishable by $^1$H-NMR spectroscopy.

A nice example is the splitting of the methine proton signal of racemic phenylethylamine in the presence of two equivalents of Taddol **1**. Without **1**, a quartet is located at $\delta$ 4.25 ppm, whereas it splits into two quartets centred at $\delta$ 3.63 ppm and $\delta$ 3.60 ppm when **1**[3] is present.

Taddols can thus be used as chiral shift reagents in NMR spectroscopy to determine the enantiomeric excess of a variety of compounds such as alcohols, amines, amino acid esters, phosphine oxides, cyanohydrins and fluoroalcohols.

Strong host/guest interactions in solution which can be identified by proton NMR might be correlated to strong interaction in the solid state and therefore to a possible successful inclusion crystallisation. The case for Taddol **1** and phenylethylamine appears to support this possibility.

To further study this possible link, some $^1$H-NMR-shift experiments have been performed with lactonitrile and four different Taddols. Taddols **2** and **4** were chosen because inclusion crystals with those Taddols and lactonitrile were already obtained in the crystallisation experiments. Taddols **1** and **10** have been chosen because no inclusion crystals were obtained and therefore no shift was expected. As expected, the NMR signal of the methine proton of lactonitrile was split in the presence of Taddols **2** and **4**. However, in the presence of Taddol **1** a splitting was also observed. This is an indication that an inclusion complex can possibly be formed with host **1** and lactonitrile, however, difficulties in nucleation may have prohibited its formation so far. Since the presence of Taddol **10** does not lead to a shift of the proton signal of lactonitrile, it does not seem to interact strongly enough with this guest and therefore the formation of inclusion crystals is less likely.

A shift of a proton signal of the guest compound in its NMR spectra with a Taddol present may be a good indication for the possible formation of inclusion complexes. However, it should be mentioned that some Taddols also crystallise together with guest compounds without showing NMR shifts. The opposite conclusion that a lack of NMR shift indicates the impossibility of obtaining an inclusion complex is by no means correct.

### 3.3.9 Prediction of resolution on basis of optical rotations

It is well known that the optical rotation of diastereomeric salts differs from the sums of the rotations of the separate components (acid anion + base cation). Kozma[46] found experimental evidence that the combination of acid and base, which shows the biggest deviation, is always the one with the lowest solubility. This observation can be explained by the fact that strong interactions between the components will lead to relatively stable complexes in solution. These will show an optical rotation behaviour deviating from uncomplexed components. As strong interaction between components will also lower solubility, a correlation between the two properties is likely. As the deviation of optical rotation may also be a good indicator for strong interactions in inclusion complexes, this was also tested for inclusion complexation with Taddol **4** and phenylethylamine. Indeed this effect was observed for the combination of Taddol **4** and L-phenylethylamine, *i.e.* the difference in the measured optical rotation and the sum of the optical rotations of the separate pure compounds is higher than in the system of Taddol **4** and D-phenylethylamine.
Initially, the optical rotation of the three pure components was measured in methanol and in chloroform, followed by those of the combinations. The results are summarised in Table 3.7.

| | | |
|---|---|---|
| TADDOL **4** | $[\alpha]_D^{20}$ = - 50.7 (c = 1; $CHCl_3$) | $[\alpha]_D^{20}$ = - 49.7 (c = 1; MeOH) |
| D-PEA | $[\alpha]_D^{20}$ = + 36.4 (c = 0.85; $CHCl_3$) | $[\alpha]_D^{20}$ = + 29.9 (c = 0.85; MeOH) |
| L-PEA | $[\alpha]_D^{20}$ = - 36.1 (c = 0.75; $CHCl_3$) | $[\alpha]_D^{20}$ = - 29.9 (c = 0.85; MeOH) |
| **4** + D-PEA | $[\alpha]_D^{20}$ = - 15.6 (c = 1.8; $CHCl_3$) | $[\alpha]_D^{20}$ = - 15.7 (c = 1.85; MeOH) |
| **4** + L-PEA | $[\alpha]_D^{20}$ = - 47.6 (c = 1.8; $CHCl_3$) | $[\alpha]_D^{20}$ = - 39.0 (c = 1.85; MeOH) |
| sum (**4**+D) | - 50.7 + 36.4 = - 14.3 | - 49.7 + 29.9 = - 19.8 |
| sum (**4**+L) | - 50.7 - 36.1 = - 86.8 | - 49.7 - 29.9 = - 79.6 |
| difference D | - 15.6 – (- 14.3) = -1.3 | - 19.8 – (- 15.7) = - 4.1 |
| difference L | - 86.8 – (-47.6) = - 39.2 | - 79.6 – (- 39.0) = - 40.6 |

**Table 3.7:** Comparison of optical rotations

The difference in the measured optical rotation and the sum of the optical rotations of the pure compounds is far higher in the system of Taddol **4** and L-phenylethylamine. Hence, a stronger interaction between L-PEA and Taddol **4** is expected leading to a lower solubility. Indeed, the L-enantiomer of the amine is preferably included in **4** (lower solubility).
It is not yet clear if this method really works in all cases, which would allow prediction of inclusion of a certain guest. Further examples should be investigated. Unfortunately, this method requires availability of the two separate enantiomers of the guest, which is difficult

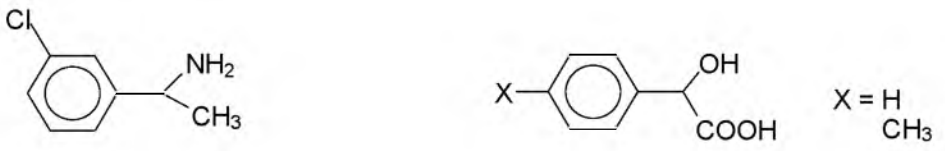
and expensive in many cases. Alternatively, if the two enantiomers of the host are available the method can be used if only one pure enantiomer of the guest is available.

The combination of looking for NMR shifts and differences in optical rotation may provide a useful tool in the search of suitable hosts. Solving the nucleation problem can be very tedious, especially if it is unsure whether a complex will be formed at all. Determination of NMR shifts and optical rotation may give an indication if efforts to solve the nucleation problem are justified in a particular case.

## 3.4 Experiments with mixtures of Taddols

### 3.4.1 Introduction

The family approach to the resolution of racemates, the so-called Dutch Resolution[54], has simplified the separation of enantiomers *via* diastereomeric salt formation tremendously. Instead of the application of a single resolving agent, a mixture of resolving agents is added simultaneously to a racemate and it is allowed to "choose" its preferred agent, meaning the least soluble diastereomeric salt will precipitate first. Surprisingly, it was found that not only a resolution with a high efficiency took place very quickly, but that the diastereomeric precipitate also contained a mixture of resolving agents in non-stoichiometric compositions. Essential for the method is the use of similar compounds. The use of randomly combined resolving agents did not give the effect obtained with combinations of structurally related resolving agents.
To summarise, Dutch Resolution is a technique to a fast resolution of racemates using mixtures of structurally related and chemically homogeneous resolving agents. An example is given in Figure 3.8.




*m*-chloro phenyl ethylamine

M-mix
*p*-substituted mandelic acids

**Figure 3.8:** Example of Dutch Resolution[54]

Application of the M-mix resolved the *m*-chloro phenylethylamine affording an *e.e.* of 99 %. The product showed a reagent ratio of 1:4 after one re-crystallisation.
Although more than one resolving agent is present in the product, a single melting point is observed in DSC measurements. This is a strong indication of the presence of solid solution

in the resolving agent part. Solid solution is therefore suggested to play an essential role in the process of Dutch Resolution, but this has still to be substantiated.
Grouping structurally related agents and thus defining the term `family´ has not yet been possible. The requirements that resolving agents must fulfil to be combined as a `family´ are not yet clearly defined.
The thought that speeding-up crystallisation may be responsible for the success of Dutch Resolution constituted a first theory, however, the latest results on crystallisation initiations indicated that the presence of a mixture of resolving agents may even hinder the start of crystallisation (of the more soluble diastereomer).[55]
Whatever the exact cause of Dutch Resolution[56] may be, its success in practice and value in the quick resolution of racemates is beyond any doubt.

With the improvement of classical resolution by the application of mixtures of resolving agents, the idea was born that a similar advantage might be possible in inclusion resolution. The application of structurally related Taddols to the resolution of neutral molecules may result in a change from "trial and error" to a reliable separation of enantiomers *via* inclusion complexation. Indeed, a single example of the application of a mixture of Taddols as resolving agent was described by the inventors of Dutch Resolution.[54]

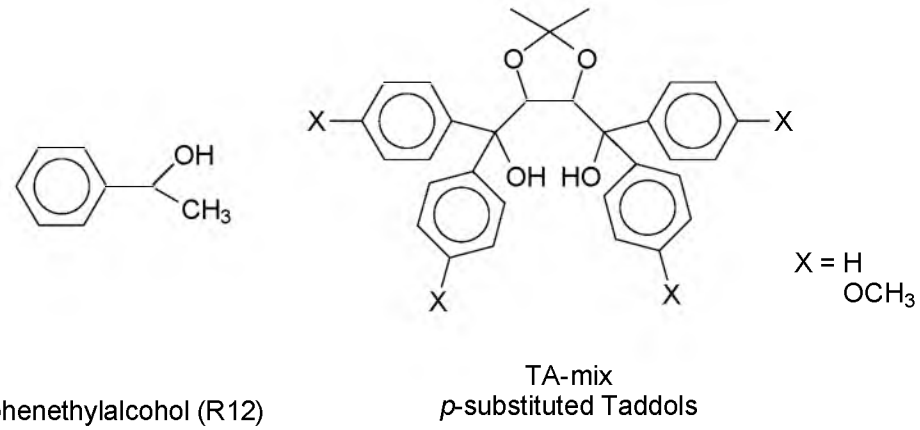


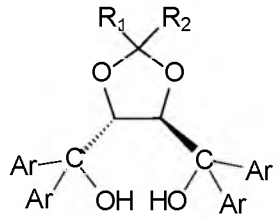

**Figure 3.9:** Example of the family approach in inclusion resolution with Taddols **1** and **7**[54]

The alcohol (R12) was resolved with the TA-mix affording an *e.e.* of 82%. The inclusion crystals contained the resolving agents in a ratio of 1:1.

This example of a family approach in inclusion resolution was taken as lead example for the investigation of whether the term "family" exists here at all and if so, how a family of resolving agents can then be described.

### 3.4.2 Inclusion experiments

The following inclusion experiments have been carried out with various mixtures of the Taddols that have already been applied individually.




$R_1,R_2$ = -methyl
Ar = -phenyl **1**
-*o*-tolyl **2**
-*m*-tolyl **3**
-*p*-tolyl **4**
-*o*-anisyl **5**
-*m*-anisyl **6**
-*p*-anlsyl **7**
-*p*-Cl-phenyl **8**

$R_1,R_2$ = -cyclohexyl
Ar = -phenyl **9**
-*p*-tolyl **10**

Ar = -*p*-tolyl
$R_1,R_2$ = -H **11**
$R_1$ = -H, $R_2$ = -phenyl **12**

**Table 3.8:** Taddols applied in the inclusion experiments

In order to form inclusion complexes with different guests, various mixtures of the Taddols have been dissolved with the respective guest compound in hexane/toluene (1:1) or heptane. They were used in a host/guest ratio of 1:1, e.g. Mix 1 (Taddol **1**,**2**,**4**, *rac*. guest) has the ratio 1:1:1:3 (see Table 3.9).

| racemic guest | Mix 1 (**1**,**2**,**4**) | Mix 2 (**2**,**3**,**4**) | Mix 3 (**1**,**9**) | Mix 4 (**5**,**7**) | Mix 5 (**5**,**6**,**7**) | Mix 6 (**2**,**5**) | Mix 7 (**4**,**7**) | Mix 8 (**4**,**10**) | Mix 9 (**9**,**10**) | Mix 10 (**4**,**10**,**11**) |
|---|---|---|---|---|---|---|---|---|---|---|
| R1 | x | ✓ | x | x | x | x | ✓ | ✓ | O | x |
| R2 | O | O | O | x | O | O | O | x | x | x |
| R3 | x | O | x | ✓ | x | x | O | O | O | O |
| R4 | x | O | x | O | O | x | O | O | x | O |
| R5 | ✓ | ✓ | x | x | x | x | x | O | x | O |
| R6 | O | O | ✓ | x | x | x | x | O | x | O |
| R7 | ✓ | x | x | ✓ | x | x | O | O | x | O |
| R8 | x | ✓ | x | x | x | x | ✓ | x | x | x |
| R9 | x | O | x | x | x | x | O | O | O | x |
| R10 | x | O | x | x | O | x | x | O | O | O |
| R11 | O | O | O | x | x | x | O | O | O | O |
| R12 | O | O | O | x | x | x | O | x | x | x |
| R13 | O | x | O | x | x | x | O | O | O | O |
| R14 | O | O | O | x | x | x | O | O | O | O |
| R15 | x | O | x | x | x | x | O | O | x | O |
| R16 | ✓ | x | ✓ | x | x | x | ✓ | O | ✓ | x |
| R17 | x | x | x | x | x | x | x | x | x | x |
| R18 | O | O | x | x | O | x | x | O | x | O |
| R19 | ✓ | x | x | x | x | x | x | x | x | x |

| racemic guest | Mix 1 (**1**,**2**,**4**) | Mix 2 (**2**,**3**,**4**) | Mix 3 (**1**,**9**) | Mix 4 (**5**,**7**) | Mix 5 (**5**,**6**,**7**) | Mix 6 (**2**,**5**) | Mix 7 (**4**,**7**) | Mix 8 (**4**,**10**) | Mix 9 (**9**,**10**) | Mix 10 (**4**,**10**,**11**) |
|---|---|---|---|---|---|---|---|---|---|---|
| R20 | ✓ | x | x | x | x | x | O | ✓ | x | x |
| R21 | x | x | x | O | O | x | ✓ | ✓ | ✓ | O |
| R22 | O | O | O | O | O | O | O | O | x | O |
| R23 | x | x | x | x | x | x | x | O | ✓ | O |
| R24 | x | x | x | x | x | x | x | x | x | x |
| R25 | x | x | x | x | x | x | x | x | x | O |
| R26 | x | x | x | x | O | x | O | x | x | O |
| R27 | x | x | x | x | x | x | x | x | x | x |
| R28 | x | x | x | O | x | x | x | x | x | O |
| R29 | x | x | x | x | x | x | x | x | x | x |
| R30 | x | x | x | x | O | x | x | O | x | x |

x crystals of pure Taddol ✓ inclusion crystals O no crystals

**Table 3.9:** Resolution experiments using various mixtures of Taddols

Most attempts to form inclusion complexes with the mixtures of Taddols and various guests were not successful. In more than 60% of the experiments pure Taddols crystallised and in approximately 30% no crystalline material was formed at all.

Unfortunately, a replication of the improvement of Dutch Resolution in resolution by diastereomeric salts in inclusion resolution could not be achieved. In contrast, the application of mixtures of resolving agents seems to hinder the formation of inclusion crystals, because less inclusion complexes were obtained compared to the experiments with the individual Taddols (22 inclusion complexes using mixtures, 38 inclusion complexes with individual Taddols).

Also another phenomenon, which is always present in Dutch Resolution, was not observed, namely the formation of mixed solid solution crystals. In all inclusion crystals obtained from the mixtures, only a single Taddol was present ($^1$H-NMR or HPLC).

Table 3.10 (next page) shows the inclusion crystals obtained and a comparison with the inclusion crystals formed in experiments with single Taddols as resolving agents.

All inclusion complexes obtained in the experiments with individual Taddols were also produced during the application of mixtures. The lower efficiencies in the mixture experiments may be attributed to the experimental practice. Here the crystals obtained after crystallisation have been analysed, whereas in the individual experiments the analyses have been performed after re-crystallisation. Yield and *e.e.* after crystallisation are approximately the same in individual as well as mixture experiments.

Four new inclusion complexes were obtained compared to the individual application.

In addition, attempts to reproduce the literature example[54] (Figure 3.9) with phenethylalcohol did not meet with success. Only pure Taddol **7** crystallised. Additional attempts to include

this alcohol using both Taddols of the mixture individually also did not lead to inclusion crystallisation.

| entry | initial sample | Taddol found | inclusion with single Taddol (see Table 3.1) | e.e. guest | yield | S |
|---|---|---|---|---|---|---|
| 41 | Mix 1 / R5 | 4 | 1, 4, 7, 9, 11 | 0 | 12% | 0 |
| 42 | Mix 1 / R7 | 4 | 1, 4, 7, 9 | 0 | 12% | 0 |
| 43 | Mix 1 / R16 | 4 | 1, 4, 7, 9, 11 | 0 | 10% | 0 |
| 44 | Mix 1 / R19 | 4* | 10 | 0 | 15% | 0 |
| 45 | Mix 1 / R20 | 2 | 2, 10, 11 | 51% | 11% | 0.2 |
| 46 | Mix 2 / R1 | 4 | 4 | 71% | 17% | 0.4 |
| 47 | Mix 2 / R5 | 4 | 1, 4, 7, 9, 11 | 0 | 13% | 0 |
| 48 | Mix 2 / R8 | 4 | 4, 10 | 78% | 26% | 0.6 |
| 49 | Mix 3 / R6 | 2 | 2, 9, 11 | 0 | 11% | 0 |
| 50 | Mix 3 / R16 | 4 | 1, 4, 7, 9, 11 | 0 | 24% | 0 |
| 51 | Mix 4 / R3 | 7* | 9 | 0 | 7% | 0 |
| 52 | Mix 4 / R7 | 9 | 1, 4, 7, 9 | 0 | 19% | 0 |
| 53 | Mix 7 / R1 | 4 | 4 | 74% | 21% | 0.5 |
| 54 | Mix 7 / R8 | 4 | 4, 10 | 72% | 23% | 0.5 |
| 55 | Mix 7 / R16 | 4 | 1, 4, 7, 9, 11 | 0 | 10% | 0 |
| 56 | Mix 7 / R21 | 2 | 2, 4 | 0 | 14% | 0 |
| 57 | Mix 8 / R1 | 4 | 4 | 75% | 21% | 0.5 |
| 58 | Mix 8 / R20 | 10 | 2, 4, 10, 11 | 55% | 14% | 0.2 |
| 59 | Mix 8 / R21 | 2 | 2, 4 | 0 | 12% | 0 |
| 60 | Mix 9 / R16 | 4 | 1, 4, 7, 9, 11 | 0 | 20% | 0 |
| 61 | Mix 9 / R21 | 10* | 2, 4 | 0 | 13% | 0 |
| 62 | Mix 9 / R23 | 10* | 2, 5 | 0 | 14% | 0 |

* no analogous inclusion complex obtained in experiments with individual Taddols

**Table 3.10:** Inclusion complexes obtained with Taddol mixtures

## 3.5 Conclusions

The number of inclusion complexes obtained from known and newly prepared Taddols as host compounds is lower than expected from examples described in literature[20-45]. Nevertheless, several new inclusion complexes have been obtained, among them some new resolutions.

It should be noted, however that the work described in the literature[20-45] usually refers to series of similar guests, which may be applied based on previously obtained lead examples.

This approach will inevitably lead to a higher success rate than when mainly unrelated compounds are tested as in this study.

Obtaining the first batch of crystals seems to constitute the major problem in inclusion crystallisation, indicated by the formation of gels, and the $^1$H-NMR shift experiments. The inability to reproduce some of the inclusion experiments described in the literature may be due to the general problem of obtaining the first crystalline material. The reproduction of successful own inclusion experiments was achieved without any problems. In contrast, if inclusion crystals are obtained once, the preparation of additional material is highly facilitated.

Taddol **4** especially was a suitable host to include and resolve a variety of smaller guest compounds. With its ability to include and resolve phenylethylamine, the main objective of the search for a suitable system for further analysis has been fulfilled.

The application of mixtures of resolving agents, compared to Dutch Resolution in classical resolution, unexpectedly did not show any improvement. The difference in the weak host/guest interactions compared to the strong interaction in salts may be an explanation.

## 3.6 Experimental section

For general remarks see section 2.4

*General procedure for crystallisation experiments with individual Taddols in solvent (see 3.3.2)*

The pure Taddols (**1**-**12**) were dissolved together with the respective guest compound (R1-30) in hexane/ toluene (1:1) or heptane and then filtered. The experiments were executed in a host/guest ratio of 1:1 at room temperature. In those cases in which crystals have been obtained, they were filtered off, washed with heptane and analysed for the presence of the respective guest compound by $^1$H-NMR analysis. If an inclusion complex was obtained, the *e.e.* of the guest included was determined (see Table 3.3).

*General procedure for crystallisation experiments under high pressure (see 3.3.4)*

The pure Taddols (**1** and **4**) were dissolved together with the respective guest compound (see Table 3.4) in heptane and then filtered. The experiments were executed in a host/guest ratio of 1:1 at room temperature using 15 kbar of pressure for five hours.

*General procedure for crystallisation experiments with individual Taddols (see 3.3.5)*

The Taddols (**1**,**4**, **9** and **10**) were dissolved in the liquid racemic guest compounds (R1, R3-4, R6, R8-15, R18-21, R25, R27-28 and R30) while boiling. The mixtures were cooled to room temperature and filtered. In those cases in which crystals have been obtained, they were filtered off, washed with heptane and analysed for the presence of the respective guest compound by $^1$H-NMR analysis. If an inclusion complex was obtained, the *e.e.* of the guest included was determined (see Table 3.3).

*Procedure for vapour sorption experiment (see 3.3.6)*

Racemic phenylethylamine was heated in a flask to 110°C while powdered Taddol **4** was kept in a small tube inside the flask, separated from the liquid amine. After 30 min the test tube was removed and analysed for the presence and then consequently the *e.e.* of phenylethylamine (*e.e.* 70%).

*Procedure for grinding experiment (see 3.3.7)*

Taddol **4** and phenylethylamine were mixed and ground in a mortar for 20 minutes. Solid host and liquid guest were combined in a ratio of 1:1 and 1:2. The solid was then washed with heptane and analysed. In both cases inclusion complexes were formed, and the amine was included affording an *e.e.* of approximately 50%.

*Procedure for $^1$H-NMR-shift experiments (see 3.3.8)*

$^1$H-NMR-shift experiments have been performed with lactonitrile and Taddols **1**,**2**,**4** and **10** with a 200 MHz apparatus. Taddols and racemic lactonitrile were combined in a ratio of 1:1 and dissolved in $CDCl_3$. The $^1$H-NMR signal of the methine proton of lactonitrile was split in the presence of Taddols **1**, **2** and **4**, but the presence of Taddol **10** does not lead to a shift.

*General procedure for crystallisation experiments with mixtures of Taddols (see 3.4.2)*

Various mixtures of the Taddols (**1**-**12**) were dissolved with the respective guest compound (R1-30) in hexane/ toluene (1:1) or heptane and then filtered. They were used in a host/guest ratio of 1:1, e.g. Mix 1 (Taddol **1**,**2**,**4**, *rac.* guest) has the ratio 1:1:1:3 (see Table 3.9). In those cases in which crystals have been obtained, they were filtered off, washed with heptane and analysed for the presence of the respective guest compound and the respective Taddol by $^1$H-NMR analysis. If an inclusion complex was obtained, the *e.e.* of the guest included was determined (see Table 3.3).

*General procedures for e.e. determination*

*General procedure for derivatisation with benzoyl chloride*

Equal amounts of guest compound, benzoyl chloride and $NaHCO_3$ were mixed for 20 min. Then a few ml heptane were added and the reaction mixture was stirred for another 20 minutes. After filtration, the solvent was evaporated and the residue analysed for *e.e.* (see Table 3.3).

General procedure for derivatisation with camphonyl chloride

5 mmol guest compound was stirred in 25 ml pyridine at 0°C while 1.36 g (6 mmol) camphonyl chloride was added slowly. After stirring over night, 2 ml MeOH were added and the solvents evaporated. After dissolving in 100 ml $CH_2Cl_2$, the product was washed with $H_2O$, 1m $NaHCO_3$ and $H_2O$, dried and analysed for *e.e.* (see Table 3.3).

## 3.7 Crystal structure data[51-53]

### 3.7.1 X-ray analysis of SMONA5

Crystals of SMONA5 (entry 10, Table 3.2) suitable for X-ray diffraction studies were obtained from heptane by slow evaporation of the solvent. A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Mo-K$\alpha$ radiation, $\omega$-2$\Theta$ scan mode. Unit cell dimensions were determined from the angular setting of 15 reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction ($\psi$-scans)[48] was applied. The structure was solved by the program CRUNCH[49] and was refined with standard methods (refinement against $F^2$ of all reflections with SHELXL97[50]) with anisotropic parameters for the nonhydrogen atoms. The hydrogen atoms of the methyl and hydroxy groups were refined as rigid rotors to match maximum electron density in a difference Fourier map. The hydrogens attached to nitrogen were taken from a difference Fourier map. All other hydrogens were initially placed at calculated positions and were freely refined subsequently.
A structure determination summary is given in Table 3.11 and a PLUTON drawing of entry 10 is shown in Figure 3.3.

| | |
|---|---|
| Identification code | SMONA5 |
| Crystal colour | transparent colourless |
| Crystal shape | regular fragment |
| Crystal size [mm] | 0.39 x 0.36 x 0.21 mm |
| Empirical formula | $C_{43}$ $H_{49}$ N $O_4$ |
| Formula weight | 643.83 g/mol |
| Temperature | 293(2) K |
| Radiation / Wavelength | MoK $\alpha$ (graphite mon.) / 0.71073 Å |
| Crystal system | Orthorhombic |
| Space group | $P2_12_12_1$ |
| Unit cell dimensions<br>(15 reflections 8.981<$\Theta$<11.468) | a=12.749(6) Å, $\alpha$=90°<br>b=12.9893(14) Å, $\beta$=90°<br>c=22.418(5) Å, $\gamma$=90° |
| Volume | 3712(2) $Å^3$ |
| Calculated density | 1.152 $Mg/m^3$ |
| Z | 4 |
| Absorption coefficient | 0.073 $mm^{-1}$ |
| Diffractometer / scan | Enraf-Nonius CAD4 / $\omega$-2$\Theta$ |
| F(000) | 1384 |
| $\Theta$ range for data collection | 2.88 - 27.48° |
| Index ranges | $0 \le h \le 16$, $-16 \le k \le 0$, $-29 \le l \le 0$ |
| Reflections collected / unique | 4730 / 4730 |
| Reflections observed | 1673 ($[I_o>2\sigma(I_o)]$) |
| Absorption correction | Semi-empirical from $\psi$-scans |
| Range of relat. transm. factors | 1.053 and 0.956 |
| Refinement method | Full-matrix least-squares on $F^2$ |

| | |
|---|---|
| Identification code | SMONA5 |
| Computing | SHELXL-97 (Sheldrick, 1997) |
| Data / restraints / parameters | 4730 / 0 / 450 |
| Goodness-of-fit on $F^2$ | 1.003 |
| SHELXL-97 weight parameters | 0.027500 0.221300 |
| Final R indices [I>2σ(I)] | $R_1$ = 0.0719, $wR_2$ = 0.0878 |
| R indices (all data) | $R_1$ = 0.2404, $wR_2$ = 0.1225 |
| Largest diff. peak and hole | 0.142 and -0.141 e.Å$^{-3}$ |

**Table 3.11:** Crystal data and structure refinement for entry 10

### 3.7.2 X-ray analysis of SMONA2

Crystals of SMONA2 (entry 13, Table 3.2) suitable for X-ray diffraction studies were obtained from a toluene/hexane mixture (1:1) by slow cooling of the solvent mixture. A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Mo-Kα radiation, ω-2Θ scan mode. Unit cell dimensions were determined from the angular setting of 16 reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction (ψ-scans)[48] was applied. The structure was solved by the program CRUNCH[49] and was refined with standard methods (refinement against $F^2$ of all reflections with SHELXL97[50]) with anisotropic parameters for the nonhydrogen atoms. The hydrogen atoms of the methyl and groups were refined as rigid rotors to match maximum electron density in a difference Fourier map. The hydrogens of the hydroxy groups were taken from a difference Fourier map. All other hydrogens were initially placed at calculated positions and were freely refined subsequently.
A structure determination summary is given in Table 3.12and a PLUTON drawing of entry 13 is shown in Figure 3.5.

| | |
|---|---|
| Identification code | SMONA2 |
| Crystal colour | transparent colourless |
| Crystal shape | soft, rough fragment |
| Crystal size [mm] | 0.38 x 0.36 x 0.26 mm |
| Empirical formula | $C_{77}$ $H_{90}$ $O_{10}$ |
| Formula weight | 1175.49 g/mol |
| Temperature | 293(2) K |
| Radiation / Wavelength | MoKα (graphite mon.) / 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | $P2_1$ |
| Unit cell dimensions<br>(16 reflections 9.636<Θ< 19.179) | a= 11.980(3) Å, α= 90°<br>b= 23.324(4Å, β= 110.849(18)°<br>c= 12.7737(17) Å, γ= 90° |
| Volume | 3335.6(10) Å$^3$ |
| Calculated density | 1.170 Mg/m$^3$ |
| Z | 2 |
| Absorption coefficient | 0.076 mm$^{-1}$ |
| Diffractometer / scan | Enraf-Nonius CAD4 / ω |

| | |
|---|---|
| Identification code | SMONA2 |
| F(000) | 1264 |
| Θ range for data collection | 2.90 - 25.61 ° |
| Index ranges | $-13 \leq h \leq 14$, $-28 \leq k \leq 0$, $-15 \leq l \leq 0$ |
| Reflections collected / unique | 6735 / 6441 [R(int)= 0.0299] |
| Reflections observed | 3145 ($[I_o>2\sigma(I_o)]$) |
| Absorption correction | Semi-empirical from ψ-scans |
| Range of relat. transm. factors | 1.046 and 0.960 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Computing | SHELXL-97 (Sheldrick, 1997) |
| Data / restraints / parameters | 6441 / 1 / 814 |
| Goodness-of-fit on $F^2$ | 1.057 |
| SHELXL-97 weight parameters | 0.060400 0.288300 |
| Final R indices [$I>2\sigma(I)$] | $R_1 = 0.0613$, $wR_2 = 0.1184$ |
| R indices (all data) | $R_1 = 0.1590$, $wR_2 = 0.1515$ |
| Largest diff. peak and hole | 0.181 and -0.177 e.$Å^{-3}$ |

**Table 3.12:** Crystal data and structure refinement for entry 13

### 3.7.3 X-ray analysis of SMONA6

Crystals of SMONA6 (entry 34, Table 3.2) suitable for X-ray diffraction studies were obtained from heptane by slow cooling of the solvent mixture. A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Mo-Kα radiation, ω-2Θ scan mode. Unit cell dimensions were determined from the angular setting of 25 reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction (ψ-scans)[48] was applied. The structure was solved by the program CRUNCH[49] and was refined with standard methods (refinement against $F^2$ of all reflections with SHELXL97[50]) with anisotropic parameters for the nonhydrogen atoms. The hydrogen atoms of the methyl and groups were refined as rigid rotors to match maximum electron density in a difference Fourier map. The hydrogen of the acid group was taken from a difference Fourier map.
All other hydrogens were initially placed at calculated positions and were freely refined subsequently.
A structure determination summary is given in Table 3.13 and a PLUTON drawing of entry 34 is shown in Figure 3.6.

| | |
|---|---|
| Identification code | SMONA6 |
| Crystal colour | transparent colourless |
| Crystal shape | rather regular rod |
| Crystal size [mm] | 0.33 x 0.16 x 0.14 mm |
| Empirical formula | $C_{39.5}\,H_{45}\,O_{5.5}$ |
| Formula weight | 607.76 g/mol |
| Temperature | 293(2) K |
| Radiation / Wavelength | MoKα (graphite mon.) / 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | $P2_1$ |

| Identification code | SMONA6 |
|---|---|
| Unit cell dimensions<br>(25 reflections 8.928 <Θ< 10.694) | a= 14.7148(11) Å, α =90°<br>b= 12.6932(10) Å, β= 94.487(19)°<br>c= 18.3412(14) Å, γ= 90° |
| Volume | 3415.2(5) $Å^3$ |
| Calculated density | 1.182 $Mg/m^3$ |
| Z | 4 |
| Absorption coefficient | 0.077 $mm^{-1}$ |
| Diffractometer / scan | Enraf-Nonius CAD4 / ω-2Θ |
| F(000) | 1304 |
| Θ range for data collection | 2.53 - 27.47° |
| Index ranges | -19 ≤ h ≤ 0, 0 ≤ k ≤ 16, -23 ≤ l ≤ 23 |
| Reflections collected / unique | 8482 / 8175 [R(int)= 0.0469] |
| Reflections observed | 3479 ([$I_o$>2σ($I_o$)]) |
| Absorption correction | Semi-empirical from ψ-scans |
| Range of relat. transm. factors | 1.084 and 0.950 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Computing | SHELXL-97 (Sheldrick, 1997) |
| Data / restraints / parameters | 8175 / 1 / 830 |
| Goodness-of-fit on $F^2$ | 1.038 |
| SHELXL-97 weight parameters | 0.074800 0.000000 |
| Final R indices [I>2σ(I)] | $R_1$ = 0.0801, $wR_2$ = 0.1524 |
| R indices (all data) | $R_1$ = 0.2098, $wR_2$ = 0.1992 |
| Largest diff. peak and hole | 0.298 and -0.248 e.$Å^{-3}$ |

**Table 3.13:** Crystal data and structure refinement for entry 34

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# 4 First phase diagrams of diastereomeric pairs of inclusion complexes

*This chapter describes the physico-chemical aspects of selected inclusion resolution experiments with Taddols as host compounds. For the first time, binary phase diagrams and a ternary phase diagram of inclusion complexes have been recorded.*

## 4.1 Introduction

Studying the properties of mixtures of diastereomeric inclusion compounds in relation to their different compositions is an essential tool in understanding the thermodynamics of the process of inclusion resolution. Thermodynamical and physicochemical data are required to gain insight into the scope and limitation of this phenomenon. The determination of phase diagrams constitutes the first step in obtaining a more detailed knowledge about the subject. Several classical resolution processes *via* diastereomeric salt formation have been described in detail regarding their physicochemical behaviour, but so far analogous analyses have not been performed for the racemate separation *via* diastereomeric inclusion complexes.

## 4.2 Binary mixtures

### 4.2.1 Phase rule[1]

Phase diagrams describe the behaviour of systems which consist of one or more components distributed in one or more phases (liquid, solid and gaseous) as a function of variables (temperature, pressure and composition). The ideal melting behaviour of the two enantiomers of a racemate is shown in Figure 4.1. The phase relations are illustrated by plotting the melting ranges as a function of the composition ($\chi$). Such a binary phase diagram shows a number heterogeneous compositions, in which the number of phases ($\phi$) as well as the number of components (C) is determined by the phase rule. The variance (v) of a system is dependent on pressure and temperature. A system containing C components and $\phi$ phases is defined by the phase rule, which states that the number of variables is $v = C - \phi + 2$. When analysing melting point diagrams, in which only liquid and solid phases are present, the influence of pressure is only minor and can therefore be neglected, leaving only composition and temperature as variables. The phase rule can then be written in the form $v = C - \phi + 1$.

### 4.2.2 Binary phase diagram[1,7,8]

Figure 4.1 shows a system of two ideally behaving components; they neither interact with each other ($\Delta H_{mix}$ = 0) nor form mixed crystals in the solid state. In such a system, the relationship between the variables and the number of phases is expressed as $v = 2 - \phi + 1 = 3 - \phi$.

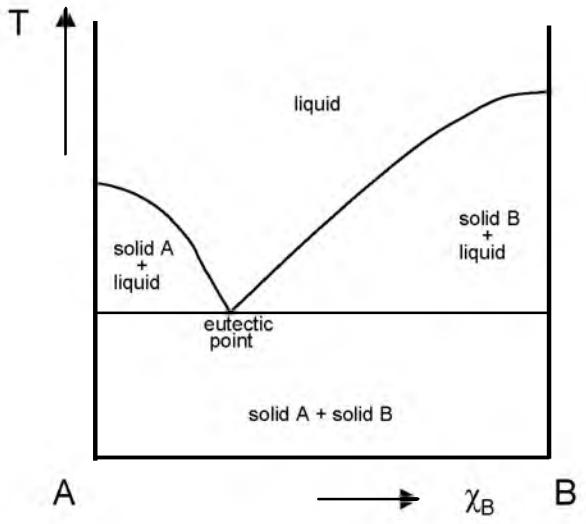



**Figure 4.1:** Binary phase diagram illustrating ideal eutectic behaviour

As a consequence, the equilibrium between the two solid compounds and the melt is only possible at a specific composition and temperature, i.e. if $\phi$ = 3, the variance of the system is zero. This is called the eutectic point. Cooling down a melt whose composition is not eutectic, only one pure compound crystallises. While crystallisation occurs, the composition of the remaining melt changes slowly to the eutectic one. At this composition the other compound also starts crystallising.

The composition of the mixture is usually described as a mole fraction of one of the constituents. If the mole fraction of **A** is $\chi_A$, consequently the mole fraction of the other compound **B** is given by $\chi_B = (1- \chi_A)$. For mixtures of enantiomers, whose molecular weights are identical, the mole fractions are equivalent to weight percent. The enantiomeric excess of each composition is given by *e.e.* = $2\chi_A - 1$ ($\chi_A > 0.5$).

Crystalline racemates can belong to three different classes: conglomerates, racemic compounds and pseudoracemates. Conglomerates consist of a mechanical mixture of crystals of the pure enantiomers. They are formed in a spontaneous resolution and are therefore often called “racemic mixtures“. This should not be confused with the so-called “racemic compounds“, which form the second and most common class of racemates. In the

crystal lattice of components belonging to this class, the two enantiomers are arranged in a well-defined regular pattern in equal quantities, so that a homogeneous phase of regular stoichiometry occurs. Finally, a more rare class is formed by the so-called pseudoracemates. There, a solid solution is formed by the two enantiomers, co-existing unordered and with variable composition in the crystal. Enantiomeric mixtures of these three different classes can be depicted in specific types of binary phase diagrams describing their properties. The melting point phase diagrams (Figure 4.2) show the characteristic behaviour of enantiomeric mixtures belonging to the different classes.

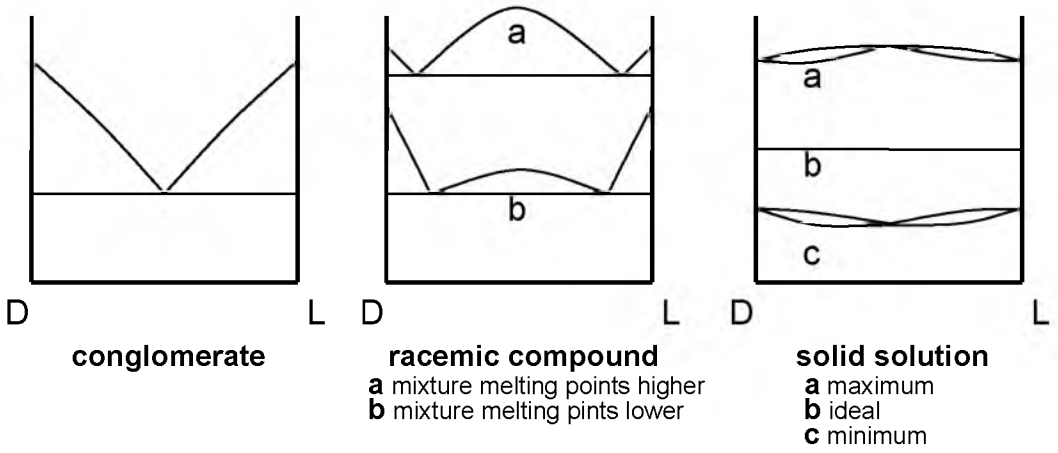



**Figure 4.2:** Melting point phase diagrams of enantiomeric mixtures

The first diagram illustrates a conglomerate. It is an equimolecular mixture of mechanically separable crystals of the two enantiomers. The relation between the temperature of the system and the composition of the liquid phase can be expressed with the Schröder-Van Laar equation. Using this equation, a mathematical calculation of the binary phase diagram of a conglomerate is possible, if the melting points and heats of fusion of the pure enantiomers are known.

$$\ln x = \frac{\Delta H_A^f}{R}\left(\frac{1}{T_A^f} - \frac{1}{T^f}\right)$$

$\chi$ : mole fraction of the more abundant compound
$\Delta H_A^f$ : enthalpy of fusion of pure compound A (in J·mol$^{-1}$)
$T_A^f$ : melting point of pure compound A (in K)
$T^f$ : melting point of the mixture of the composition $\chi$ (in K)
$R$ : gas constant (8.31451 J·mol$^{-1}$·K$^{-1}$)

**Equation 4.1:** Simplified Schröder-Van Laar equation[1]

If the system fulfils the requirements of immiscibility in the solid state and ideal behaviour in the liquid state, a calculation of the diagram using the simplified Schröder-Van Laar equation is possible.

The second diagram illustrates the behaviour of a racemic compound. The two enantiomers crystallise together and are both present in a unit cell. Several different phase diagrams of racemic compounds are known, varying strongly in shape. Class **a** illustrates the curve's shape, if the mixture of racemic composition melts at higher temperature than the pure enantiomers do, whereas in class **b** the lower melting behaviour of such a mixture is shown. The central part of the diagram, describing the melting behaviour of a racemate, can be calculated using an equation developed by Prigogine and Defay.[1] The remaining parts of the diagram can be calculated by the Schröder-Van Laar equation. This equation can be used to calculate those binary systems whose crystalline addition compound contains the two compounds in a ratio of 1:1.

$$\ln 4x(1-x) = \frac{2\Delta H_R^f}{R}\left(\frac{1}{T_R^f} - \frac{1}{T^f}\right)$$

$\chi$ : mole fraction of the enantiomer with melting point $T^f$

$\Delta H_R^f$ : enthalpy of fusion of racemic compound (in J·mol$^{-1}$)

$T_R^f$ : melting point of racemic compound (in K)

$T^f$ : melting point of the mixture of the composition $\chi$ (in K)

$R$ : gas constant (8.31451 J·mol$^{-1}$·K$^{-1}$)

**Equation 4.2:** Prigogine - Defay equation[1]

The last of the three phase diagrams illustrates solid solution behaviour; that means randomly mixed crystals of the two enantiomers are formed. Three different classes of solid solution behaviour can be obtained, well distinguishable by their phase diagrams. In class **a** and **c** a maximum or minimum melting point for the racemate is observed, whereas for an ideal solid solution, class **b**, each mixture of the enantiomers melts at a constant temperature independent of its composition. This implies an enthalpy of mixing ($\Delta H_{mix}$) of zero in the solid phase. Binary diagrams of diastereomers are nearly analogous to those of enantiomers, but in general lack the mirror symmetry. The ultimate efficiency of a resolution procedure is fully determined by the eutectic composition in a ternary solution phase diagram (see section 4.4). In most cases, however, a near equivalence between the eutectic composition in the melt and in a solution is given. In a resolution procedure, the eutectic composition of a melt is for that reason often a suitable indicator of the efficiency of a resolving agent. However, since possible strong solute-solvent interactions have not been taken into account, which could surely alter the eutectic composition. Hence, the information provided by binary phase diagrams should be used with some caution.

### 4.2.3 Experimental construction of binary phase diagrams

The experimental construction of binary diagrams requires data furnished by measuring heating curves. Traditionally visual observation of the melting behaviour has been used, but such curves can be obtained nowadays more accurately using differential scanning calorimetry (DSC). Using DSC, the enthalpies and temperature ranges of phase transitions in a pure compound or a mixture can be determined. DSC measures the absorption or release of heat by the sample as a function of temperature as the sample is heated or cooled. Two cells, a sample cell and a reference cell, are heated or cooled simultaneously (Figure 4.3). A detector measures the difference in energy that is necessary to keep the two cells at the same temperature while an increase or decrease of temperature is induced. The instrument detects the exchange of energy per time unit. Any phase transition will lead to a temperature difference between sample and reference, which will be compensated by adjusting the difference between the energy flow to the sample and reference.

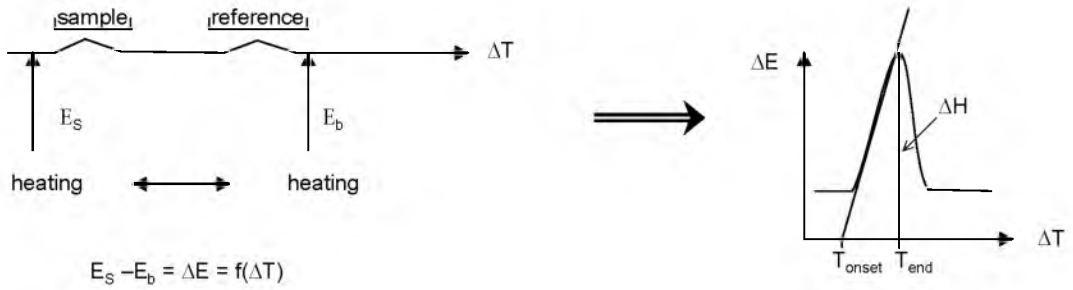



**Figure 4.3:** Energy curve obtained by differential scanning calorimetry

The output is an energy curve, showing the energy absorbed or evolved by the sample as a function of temperature. Information about the temperature range in which the transition takes place is given by a signal whose area (integral) gives the phase transition enthalpy ($\Delta H$). $T_{onset}$ presents the true melting point of the compound or mixture, which is given by the intersection of a drawn line along the ascending edge of the fusion peak and the baseline.

In order to construct a binary phase diagram for a system of two compounds, several mixtures of known compositions of the two compounds are required. To obtain accurate and reproducible results, the mixtures used should be very homogeneous. Different techniques to achieve this can be employed. In most cases, mixtures are carefully ground in a mortar to ensure even mixing. Mixing may be improved by the addition of a small amount of a volatile solvent (slurry formation), which is later removed by evaporation. A nearly homogenous mixture is obtained by evaporation of a solution of the mixture. However, this approach is limited to a few cases, as it can only be applied to mixtures which crystallise again upon evaporation.

# 4.3 Binary phase diagrams of diastereomeric pairs of inclusion complexes

## 4.3.1 Introduction[1]

In contrast to enantiomers, diastereomeric pairs (salts or inclusion compounds) have different physical properties. An analysis of their thermodynamics should help in acquiring a better understanding of resolutions. To date, "trial and error" still constitute the daily practice in inclusion resolution. No prediction can be made about the conditions, which both, host and guest, must fulfil in order to form one crystal lattice together.

Examples in the literature (see chapter 2, appendix) have shown that the shape of the host and its ability to form hydrogen bonds are of primary importance. The majority of host compounds have a rigid structure provided with scissor-like endings and polar functionalities as suitable hydrogen donors and acceptors. The Taddol-like host compounds additionally contain aromatic groups at their endings, which are believed to be responsible for the formation of the lattice backbone. Depending on the respective guest compound, the fairly rigid host is flexible in its intermolecular arrangement. The same host can form channels, cavities or layers in which the different guests are included. This behaviour complicates an understanding of the scope and limitation of any resolution process. Predictions of host-guest combinations of this type are virtually impossible at the moment. A better understanding of the phenomenon of inclusion resolution, which could hopefully lead to rationalisation and finally to design new resolutions is desirable.

An additional problem is the existence of solid solution or polymorphism. If solid solution is present in a resolution process, an eutectic may not exist and an understanding of the process will be aggravated. A large number of re-crystallisations will then be required for purification. In the weaker bond inclusion complexes, which lack the strong electrostatic interaction of diastereomeric salts, such solid solution behaviour, is conceivably more common. To determine a phase diagram of an example of inclusion resolution, the preparation of mixtures of compounds in exactly known ratios of a wide range of compositions is required. This can only be achieved, if the two diastereomers of an inclusion compound are available in pure form. In all the available literature (see chapter 2, appendix), only information on the least soluble host-guest diastereomer is given. No examples have been published about the ability of a host to include the two antipodes of a guest compound separately, i.e. the existence of both pure diastereomers.

### 4.3.2 Results

During the experiments performed with the Taddols as host molecules, two pairs of diastereomeric inclusion compounds were obtained that were suitable for further thermodynamic investigations. The Taddol **4** (Figure 4.4) has the ability to include the two enantiomers of phenylethylamine as well as the two enantiomers of *trans*-2-methoxycyclohexanol separately. For the first time a description and comparison of both diastereomers of an inclusion compound and the construction of phase diagrams became possible.

*Taddol 4 and racemic phenylethylamine*

Since Taddol **4** can include both commercially available enantiomers of phenylethylamine separately, leading to two diastereomeric crystals, this system was chosen as the first example for further investigations into the physical chemistry of inclusion compounds.

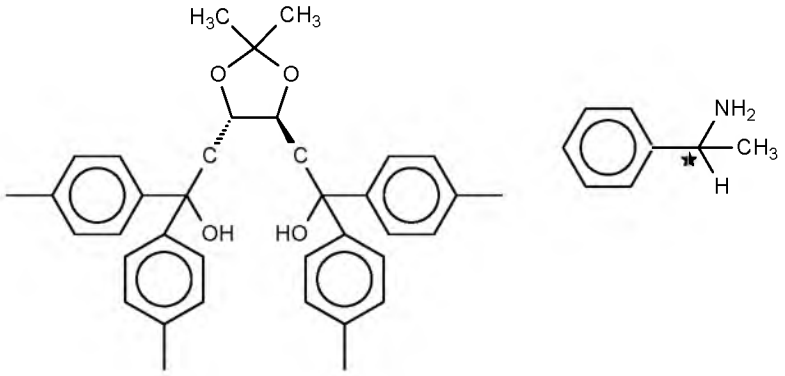



**Figure 4.4:** *(R,R)*-Taddol **4** and racemic phenylethylamine

The inclusion crystals with the two different sets of enantiomers, as well as mixtures of these crystals of different enantiomeric composition, were investigated with the aid of differential scanning calorimetry. Initially the melting points of the pure inclusion compounds, from now on called D (*(R,R)*-Taddol **4** + D-phenylethylamine) and L (*(R,R)*-Taddol **4** + L-phenylethylamine)* were measured, followed by the melting points of several mechanically prepared mixtures of them. Before measuring the melting points, the pure compounds had been re-crystallised three times from heptane in order to be entirely sure about their purities. The mixtures were prepared by accurately weighing the two solid compounds and grinding them in a mortar to mix them evenly. The addition of solvent or the convenient preparation of homogeneous mixtures from solutions prepared in volatile solvents, which are removed later on, is impossible. The effect of resolution with addition of solvent or working in solution could

* It should here be noted that (*R*) is the configuration of D-phenylethylamine and consequently (*S*) the one of L-phenylethylamine. However, the D/L nomenclature will be used throughout this thesis.

not be excluded. This should have an undesired effect on the composition to be analysed, since it may result in a new crystal composition, different from the original one.
Besides these mechanical mixtures, mixtures of the two enantiomers of phenylethylamine in different compositions were prepared and then combined with Taddol **4** in heptane. The enantiomeric excesses of the precipitated crystals have been determined followed by analysis with differential scanning calorimetry. However, using this method only a limited range of mixtures could be obtained.
Since D and L are diastereomers, they differ in their physical properties, i.e. their melting points. The melting point of pure D is 103.2 °C and that of pure L is 143.2 °C.

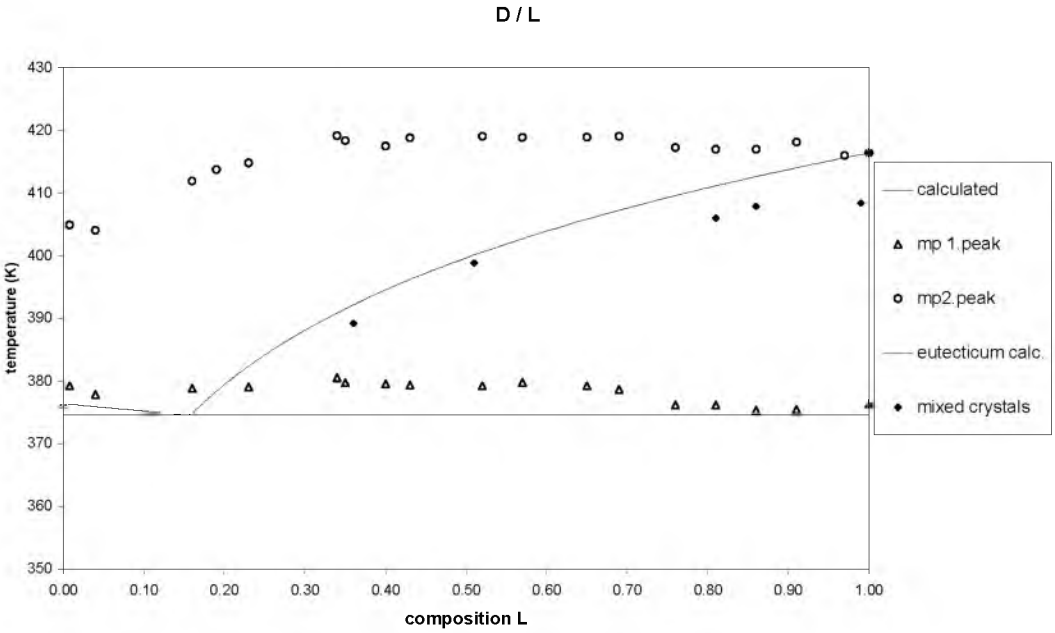



**Diagram 4.1**: Binary Diagram of D (Taddol **4** + D-phenylethylamine) and L (Taddol **4** + L-phenylethylamine)

Two separate melting points were found for each mechanically prepared mixture, indicated by the dots. The two lines show the calculated theoretical curves based on the Schröder-Van Laar equation. For the mixed crystals obtained from solution, only a single melting point (diamonds) was observed.
The calculated curve shows the melting behaviour of a conglomerate with the eutectic at an *e.e.* of 70% D-phenylethylamine. The *e.e.* determined after a single crystallisation from the racemic mixture was 77%, wherein the L-amine was preferably included. This experimental result does not correspond with the theoretically calculated enantiomeric excess. Since a description of this system using the Schröder-Van Laar equation is impossible and the equation of Schröder-Van Laar can only be fully applied for eutectic systems (see 4.1.1). This system of diastereomers does not belong to the group of conglomerates.

Two different melting points were measured for each mechanically prepared mixture: one at approximately 105°C and the other one at approximately 145°C. It seems, as if the two diastereomeric compounds were melting separately, without influencing each other; a rather puzzling result as this is physically impossible. While two compounds in contact with each other are melting, there is always a mutual interaction, as expressed e.g. in the Schröder-Van Laar equation (Equation 4.1). However, a repetition of the melting experiments gave analogous data, resulting in an identical diagram. Hence, reproducibility of the results was proven. This unexpected phenomenon could be caused by evaporation of the included amine out of the inclusion compound, which accounts for the observed peaks in the DSC. Upon evaporation of the guest, the combined crystal lattice collapses leaving liquid Taddol **4** behind. Depending on the stability of the crystal lattice, each enantiomer of the amine evaporates at a different temperature. Two "melting points" are therefore detected for each mixture, however, no real melting points were actually measured, instead an evaporation of the amine included leaving molten host behind. Hence, no real binary phase diagram could be recorded using the mechanically prepared mixtures.

The situation with the mixed crystals obtained from solution is quite different. Only one melting point was measured for each of the mixed crystals. The diamond shaped dots standing for only a single melting point per mixed crystals thus indicates a solid solution behaviour between the two phenylethylamine / Taddol diastereomers. Also in this case probably no real melting points were measured, but again an evaporation of the guest, leaving the molten host. Due to the solid solution of the amine in the crystal, now a continuous range of stabilities is observed.

In summary, the first binary phase diagram of an inclusion resolution process apparently resembles solid solution behaviour, but is not related to true melting behaviour. Instead it reflects the disruption of the inclusion complex by evaporation of the guest compound. For this system, the use of mechanical mixtures was impossible and did not lead to the desired melting point diagram.

*Racemic Taddol **4** and D-phenylethylamine*

Searching for similarities in other inclusion resolution processes, a second phase diagram was recorded.

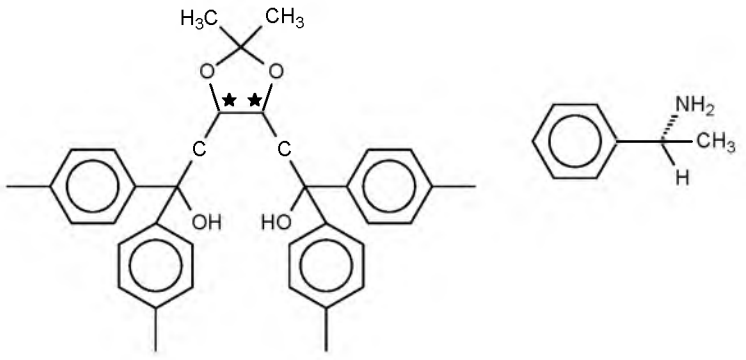



**Figure 4.5:** Racemic Taddol **4** and D-phenylethylamine

Whereas in the D/L phase diagram enantiopure host **4** and the two enantiomers of phenylethylamine have been combined, now mixtures of the diastereomeric inclusion compounds of the D-enantiomer of the amine and both enantiomers of Taddol **4**(*R,R*) and **4**(*S;S*) were investigated (reciprocal resolution).

Firstly the melting points of the pure inclusion compounds, from now on called R for (**4**(*R,R*) + D-phenylethylamine) and S for (**4**(*S;S*) + D-phenylethylamine), were measured followed by the melting points of several mixtures of them. Before performing the melting experiments, the pure compounds had been recrystallised three times from heptane.

The mixtures were prepared by accurately weighing the two solid compounds, and then grinding them evenly in a mortar. The binary diagram (Diagram 4.2) illustrates a similar melting behaviour as was observed for the reciprocal resolution.

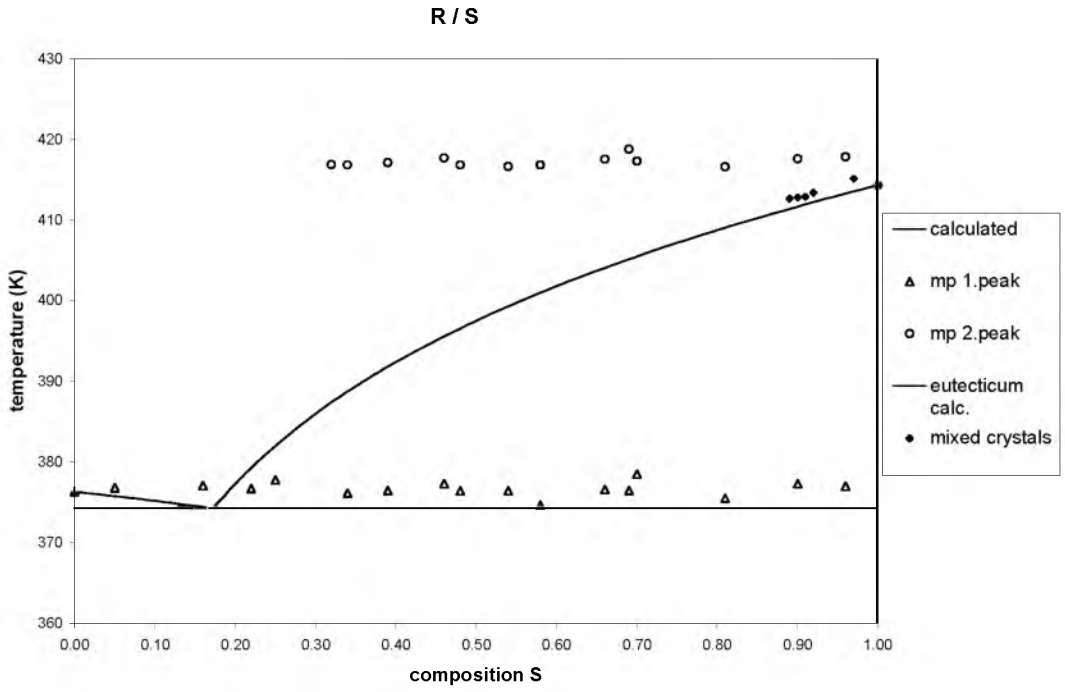



**Diagram 4.2:** Binary Diagram of R ((*R,R)*-Taddol **4**+ D-phenylethylamine) and S ((*S,S)*-Taddol **4**+ D-phenylethylamine)

The melting point of pure R is 103.2°C and the melting point of pure S is 141.9°C. As in the previous example, two different melting points were measured for most of the mixtures (scattered lines), except for the mixtures containing a little amount of S, where only one melting point was obtained. The lower melting point was always at approximately 105°C, in the same area as the melting point of pure R. The second melting point was always found in the range of 143°C, which is about one degree higher than the melting point of pure S. The two

lines illustrate the calculated curves of a conglomerate. The diamond shaped dots represent the single melting point obtained for each mixed crystal.
The diagrams of both examples, the previously discussed D/L mixture and S/R mixture resemble a similar behaviour. Once more, the analysis of mechanically prepared mixtures did not lead to a proper binary phase diagram and a calculation by the Schröder-Van Laar equation is impossible.

*Taddol **4** and racemic trans-2-methoxycyclohexanol*
Finally, a third system with a different guest compound, was investigated in the same way.

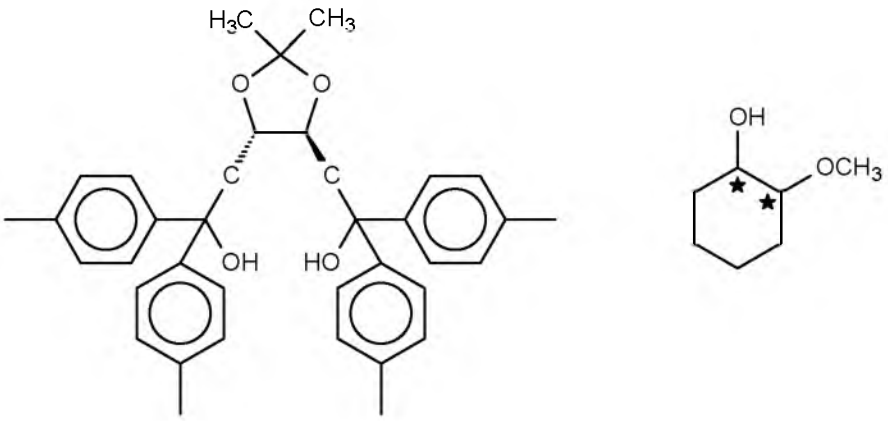



**Figure 4.6:** *(R,R)*-Taddol **4** and racemic *trans*-2-methoxycyclohexanol

Since Taddol **4** is able to resolve racemic *trans*-2-methoxycyclohexanol with an *e.e.* of 94% after recrystallisation and both diastereomeric inclusion compounds could be obtained, this system was chosen for further investigations. However, the pure enantiomers of *trans*-2-methoxycyclohexanol were not as easily accessible as those of phenylethylamine. A resolution of the alcohol *via* inclusion in Taddol **4**, proved to be the only possible manner to obtain separation of the two pure enantiomers.
The mixtures were prepared and the experiments were performed as described before. From now on the pure diastereomeric inclusion compounds will be called (S,S) for ((*R,R*)-Taddol **4+** (*S,S*)-*trans*-2-methoxycyclohexanol) and (R,R) for ((*R,R*)-Taddol **4+** (*R,R*)-*trans*-2-methoxycyclohexanol).

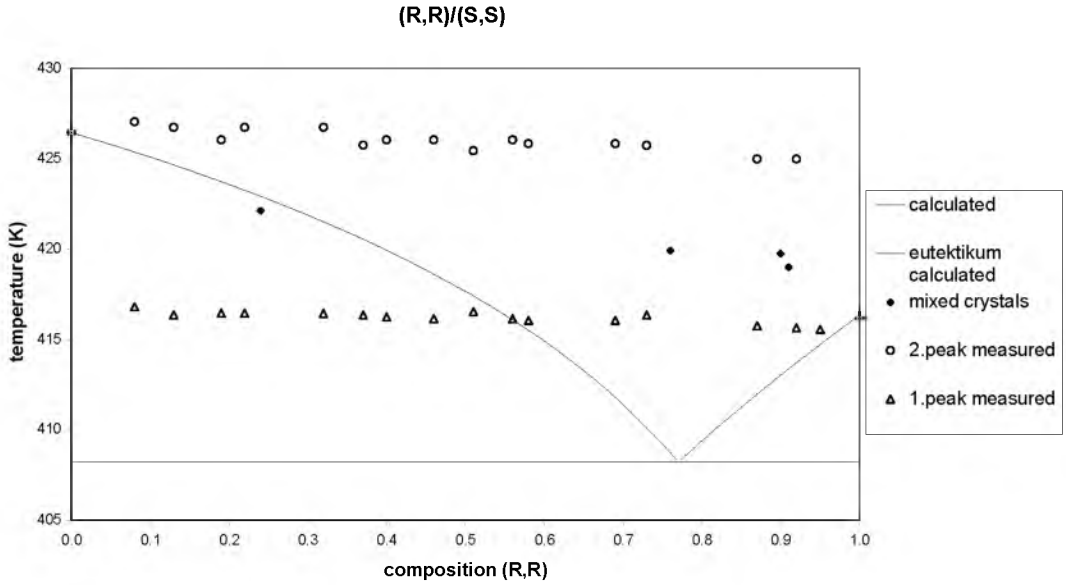



**Diagram 4.3:** Binary Diagram of (R,R) (Taddol **4** + (*R,R*)-*trans*-2-Methoxycyclohexanol) and (S,S) (Taddol **4** + (*S,S*)-*trans*-2-Methoxycyclohexanol)

Once more, an atypical binary phase diagram was recorded for this system. The apparent melting point of pure (R,R) is 143.2°C and the apparent melting point of pure (S,S) is 153.3°C.

As seen previously, two different "melting points" were found for all of the mechanically prepared mixtures. The lower "melting point" was always at approximately 142°C, which corresponds to the melting point of pure (R,R). This is indicated by the triangle shaped dots. The second "melting point" was always found in the area of 154°C, which is about one degree higher than the "melting point" of pure (S,S). It is drawn scattered. The two lines show the calculated curves of a conglomerate with the eutectic at an *e.e.* of 77% (*R,R*)-*trans*-2-methoxycyclohexanol. The *e.e.* determined after a single crystallisation from the racemic mixture was 68%, however the (*S,S*)-enantiomer was included preferably. The diamond shaped dots represent the single melting point obtained for each mixed crystal. This experimental result does not correspond with the theoretically calculated enantiomeric excess, as description of this system using the Schröder-Van Laar equation is impossible. Again, not the melting behaviour was measured, but the dissociation of the inclusion complexes. Consequently, the Schröder-Van Laar equation cannot be applied here and no conclusions can be drawn considering the nature of the mixes.

### **4.3.3** Conclusions

Taddol **4** is a good resolving agent for the studied compounds since high *e.e.*'s were achieved after just one or two re-crystallisations. This indicates conglomerate behaviour, as it is common in classical resolution *via* diastereomeric salts.

However, the attempts to construct binary melting phase diagrams failed, since upon heating the inclusion compounds no true melting points were observed, but the dissociation of the inclusion compound. Hence, with DSC a combination of the heat dissociation of the inclusion complex and the heat of evaporation of the guest compound was determined. Nevertheless, solid solution behaviour was indicated by the results of the measurements of the decompositions of mixed crystals with different compositions. Clearly, the Schröder-Van Laar equation is not applicable in these cases.

As these constitute the first examples of attempts to construct binary phase diagrams of inclusion resolution, it is not yet possible to conclude, if this behaviour is general in inclusion resolutions. Determination of further binary phase diagrams is required in order to obtain a more complete picture.

Hence, the construction of a binary diagram of diastereomeric inclusion crystals is not without problems and complications, as can be learned from the three examples analysed. The first problem is the availability of the two diastereomeric inclusion compounds. It is uncertain, whether both diastereomers can be formed at all with a specific host compound or, if the host is only able to include one enantiomer. It was not possible to obtain a melting point phase diagram using mechanically prepared mixtures, as is possible for mechanically prepared mixtures of diastereomeric salts. Reliable dissociation data were only possible to achieve by analysing mixed crystals, which themselves are often difficult to obtain.

If a solvent is present, a ternary diagram can also be used to describe the properties of diastereomers.

## 4.4 Ternary mixtures

### 4.4.1 Ternary phase diagrams[1]

The graphic representation of a heterogeneous system consisting of a liquid phase and a saturated solution equilibrated with several solid phases is called a solubility diagram. Ternary diagrams can be used to represent the relative percentage of three components (two solids and one solvent).

A full phase diagram of three components can be represented in a triangular prism in which the vertical axes describe the temperature (Figure 4.7, left). Each of the three faces of the diagram constitutes a binary phase diagram (here all combinations are ideal conglomerates).

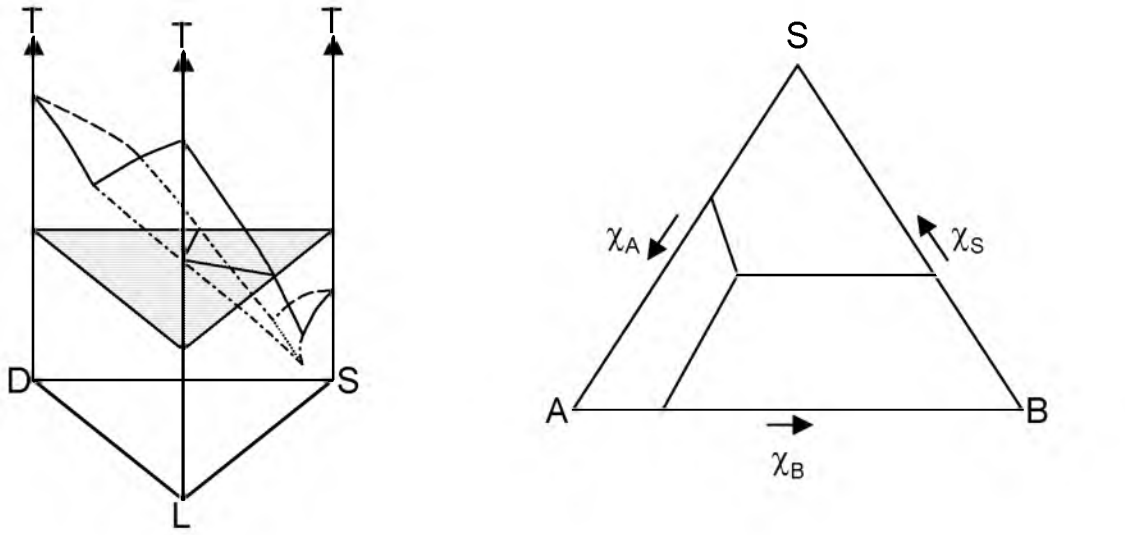



**Figure 4.7:** Ternary phase diagram

The three-dimensional diagram can be projected into a plane, by cutting at a certain temperature. The obtained triangle (Figure 4.7, right) represents an isothermal ternary diagram. The vertexes represent the pure compounds; a point located at one side belongs to the binary diagram. A point inside the triangle represents any mixture of the three components at this temperature. A line drawn parallel to one of the axis represents compositions in which one compound remains constant, whereas any line drawn straight from a vertex represents mixtures, in which the ratio of two compounds remains constant.
As mentioned earlier for binary phase diagrams, three different classes of enantiomeric mixtures exist, each showing a characteristic behaviour, which can be pictured in ternary phase diagrams.

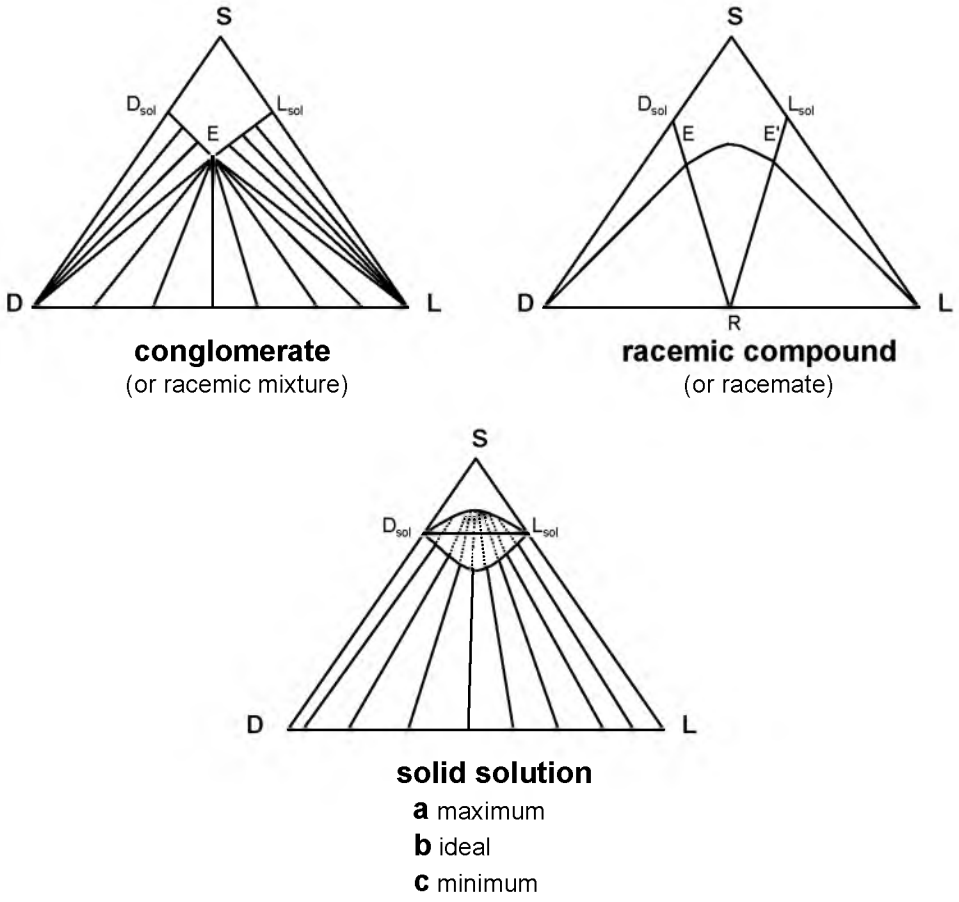


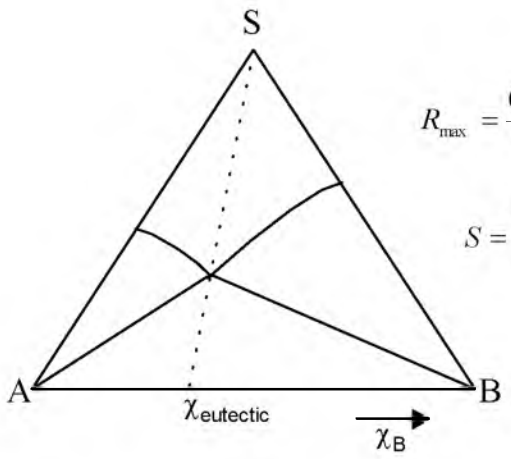

**Figure 4.8:** Solubility diagrams of enantiomers[3]

The points $D_{sol}$ and $L_{sol}$ represent the solubilities of the pure enantiomers at a given temperature. For an achiral solvent ($D_{sol}$ = $L_{sol}$) the diagram will be symmetrical. The solubility diagram of a conglomerate is divided into two parts. The upper part represents unsaturated solutions of the pure compounds in the solvent, whereas the lower part represents equilibriums of one or two solid phases with a saturated solution. According to the phase rule, the variance of this ternary system is $v = 3 - \phi + 1 = 4 - \phi$. This means, that the composition of the saturated solution in equilibrium with two solid phases at a certain temperature is fixed. This is called the eutectic composition or simply eutectic.

It should be noted, that the relative stabilities of all types, conglomerate, racemic compound and solid solution, are dependent on the temperature. A transformation from one into the other at a certain temperature is possible. As a result, more complicated phase diagrams are obtained. Various other deviations from the above described ideal phase diagrams occur, for further details see reference[1].

If D and L represent diastereomeric salts or inclusion crystals, the composition of the

eutectic determines the efficiency **S** of the resolving agent and the maximum yield $\mathbf{R_{max}}$ obtainable in a single crystallisation.




$$R_{max} = \frac{0.5 - \chi_{eu}}{1 - \chi_{eu}} \cdot 100\% \qquad (R_{max} = 0 - 50\%,\ \chi_{eu} < \chi_B)$$

$$S = \frac{1 - 2\chi_{eu}}{1 - \chi_{eu}} \qquad (S = 0 - 1,\ \chi_{eu} < \chi_B)$$

**Figure 4.9:** Determination of maximum yield $\mathbf{R_{max}}$ and efficiency **S** of a resolution

Going from the racemic composition ($\chi_B$ = 0.5) to the isolation of a pure compound (B), the equations depicted in

Figure 4.9 can be used to calculate the maximum yield and the efficiency of a resolution process. $\chi$ is the molar fraction of the least soluble diastereomer and $\chi_{eu}$ the eutectic composition. The more eccentric the eutectic, the more successful the resolution.

The second diagram in Figure 4.8 illustrates the solubility diagram of racemic compounds. The composition of the mixtures are fixed according to the phase rule at two points, E and E'. At these equilibria, the system contains three phases: an excess of solid enantiomer, the solid racemic compound and the saturated solution.

The third diagram in Figure 4.8 represents again the less common case of solid solution. The two compounds crystallise together in one single mixed crystal, forming a single homogenous phase. With the saturated solution as the second phase at constant pressure and temperature, the variance of the system is still equal to 1. As a consequence, an interdependency of the composition of the crystals and the composition of the solutions occurs. Every composition of the saturated solution corresponds to one specific composition of the crystals.

The three different types of solid solution solubility diagrams are combined in one diagram. Figure 4.8 **A** shows a diagram in which the mixtures' solubilities are higher than those of the pure compounds. They are equal in **B** and lower in Figure 4.8 **C**.

In many cases, triangular diagrams are difficult to interpret since the solvent, mainly present in each mixture is analysed. The area of interest of the solubility curves can be enlarged or the quantities of components D and L can be related to a known amount of the solvent.

### 4.4.2 Experimental construction of ternary phase diagrams[1]

In order to construct a ternary phase diagram for a system, various mixtures of known composition with varying quantities of the three compounds are required.

Each compound must be weighed accurately in the same test tube and then mixed. The use of well-closed test tubes is essential, since the samples must usually be shaken or stirred at a certain temperature for several days to obtain equilibrium. A thermostatic water bath with a shaker can be used to keep a certain temperature while attaining the equilibrium. The equilibrium can be attained from two different directions to ensure the reproducibility of the results. On the one hand, the samples are heated until all solid is dissolved, inducing the crystallisation from a supersaturated solution. On the other hand, the samples can be simply shaken at the selected temperature for a certain time, i.e. from an under-saturated solution. After the equilibrium is reached, the concentration of each component in the specific amount of solvent must be determined accurately and in a straightforward manner. When using large quantities of material, solvent and solute can be determined by evaporation of the solvent after having weighed the solution and then weighing the dry solute. In the case of smaller quantities, the composition must be determined by common methods such as HPLC, GC, etc., after a calibration curve for each component has been recorded. From the known composition of the initial mixture and the composition of the liquid, the composition of the solid can now be determined based on the tie line (see Figure 4.10).

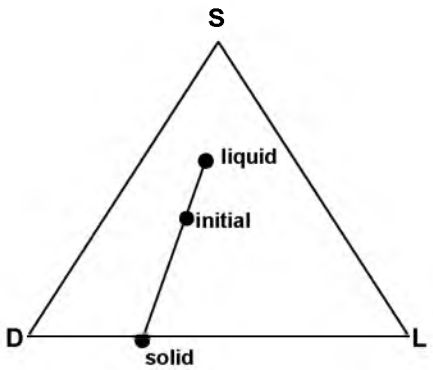



**Figure 4.10:** Tie line illustrating the initial, liquid and solid composition of one sample

Since all three points (liquid composition, initial composition and solid composition) must lie on the tie line, an extrapolation to the solid composition is possible. This composition can so be calculated. However, it is advisable to also measure the composition of the solid. If the initial and the liquid compositions are close together, small errors in these values can especially result in large errors of the composition of the solid.

# 4.5 Ternary phase diagram of a diastereomeric pair of inclusion complexes

## 4.5.1 Introduction

In view of the difficulties in obtaining binary phase diagrams of diastereomeric pairs of inclusion complexes, the subsequent study of the construction of a ternary phase diagram of the D/L inclusion system with hexane as solvent was undertaken. The diastereomer (*(R,R)*-Taddol **4** + D-phenylethylamine) is again called D, and L stands for (*(R,R)*-Taddol **4** + L-phenylethylamine).

## 4.5.2 Results

The inclusion crystals with the two enantiomers, as well as mixtures of these crystals of different enantiomeric composition, were dissolved in hexane and then stirred in a water bath at 22°C for three days. The concentration of Taddol **4** was determined by HPLC-analysis and the *e.e.* of the amine in solution was determined by GC after derivatisation with camphanoyl acid chloride. In this way the concentrations of both, D and L, in the respective liquid phases could be determined. Knowing the concentrations in the liquid phase as well as the initial ones, the concentration in the remaining solid material could be easily calculated. However, for verification, the *e.e.*'s of the amines in some solid phases also have been determined and they were in agreement with the corresponding calculated ones. Three independent series of mixtures have been used to construct the following diagram in order to ensure the accuracy of the results.

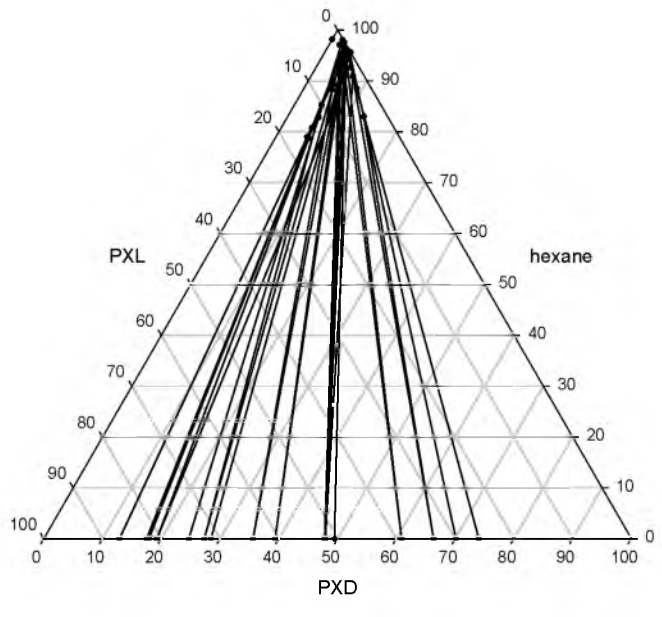



**Diagram 4.4:** Ternary phase diagram Taddol **4** / phenylethylamine / hexane

The solubility diagram of the Taddol **4** / phenylethylamine / hexane system clearly shows, in accordance with the corresponding binary phase diagram, solid solution behaviour. In the enlarged segment (Diagram 4.5) no eutectic point can be observed.

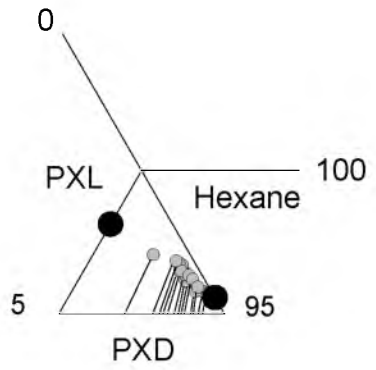



**Diagram 4.5:** Enlarged segment of the ternary phase diagram 4.4

Unfortunately, due to a large difference in the solubilities of the two diastereomers, major practical difficulties were encountered in the region with a high content of L. The initial amount of each solid used should be high enough to ensure a solution saturated in both stereoisomers. Consequently, no data could be obtained for this part of the diagram.

### 4.5.3 Conclusions

The shape of the ternary phase diagram of the Taddol **4** / phenylethylamine / hexane system fully confirms the solid solution behaviour. That means, the co-inclusion of both enantiomers of the amine together into the chiral cavities formed by Taddol **4**. Since this constitutes the first solubility phase diagram of diastereomeric inclusion complexes, no general conclusions concerning the behaviour of inclusion resolution can be drawn yet. A comparison can only be made with solubility diagrams of diastereomeric salts[4-6], from which a few ternary solid solution diagrams are known in the literature. It was found[1], that solid solution between diastereomeric salts is not as rare as solid solution between enantiomers, because the presence of the same counterion in both diastereomers increases their similarity compared to enantiomers. Analogous conclusions can be drawn for diastereomeric inclusion complexes. The presence of the same, neutral host in both complexes in equal proportions, leads also to a better similarity. In contrast to diastereomeric salts, the flexibility in diastereomeric inclusion crystals should be larger due to a weaker interaction between host

and guest molecule. The chance of observing solid solution behaviour in inclusion complexes might therefore be even higher. However, these are yet only suppositions, many additional solubility diagrams of diastereomeric inclusion complexes are needed to obtain a more complete picture.
In the study of inclusion resolution processes, the construction of ternary phase diagrams is preferred over binary diagrams, as the former leads to a better understanding by also covering all solvent effects. This is especially true in the present cases, since the constructions of the binary diagrams are impossible due to the instability of the complexes. The construction of ternary phase diagrams does not necessarily require more experimental effort than the construction of binary diagrams. In contrary, the difficulty in obtaining suitable homogenous mixtures for binary diagrams does not occur for ternary diagrams. The development of a suitable analytical methods to determine the composition of the mixture is the only disadvantage in the construction of ternary phase diagrams.

## 4.6 Powder diffraction and X-ray analyses

To obtain additional information about the nature of the various mixtures of D and L, powder X-ray analysis was applied as well. Powder diffraction reflects the bulk composition of a compound. It is a fast and reliable tool for the identification of compounds, its application in the analysis of geological materials is especially of importance. Apart from the basic identification, XPD data can be used to determine the proportion of compounds in a mixture. It is a useful analysis technique for those compounds, which are too finely grained to be identified by X-ray spectroscopy, as it is the case for D, which is a powder. However, the powder diffraction of D and L results in identical data. Therefore distinguishing between them by powder diffraction and determination of the nature of mixed crystals is impossible. The resemblance between D and L is again indicated. The pure host compound Taddol **4** itself is amorphous and for that reason an analysis of this material results in a different spectrum. Apparently this compound is not able to crystallise without a suitable guest compound forming a stable crystal lattice.
As it is impossible to determine the nature of mixed crystals of D and L by XPD, an attempt was made to determine the full crystallographic structures using X-ray analysis. In contrast to powder diffraction, X-ray analysis is performed on a single crystal. A disadvantage of single crystal X-ray analysis is always the risk that the selected crystal is not representing the bulk of the material. However, it should be possible to distinguish between D and L with this technique and look for small differences in the otherwise similar crystal lattices. Suitable crystals of L could easily be obtained, whereas pure D, despite much effort, could only be obtained as a powder. Ultimately, suitable crystals were obtained containing 65% D. Also crystals containing 50% of both, D and L could be grown. These three crystals were subjected to single crystal X-ray analysis. Hence, an analysis of mixed crystals (DL) with a

high proportion (65%) of the D-amine included, results in a X-ray pattern for D. The crystals with an equal amount of the two compounds clearly showed solid solution of the amine. Amine sites are randomly occupied by D-amine and L-amine. The X-ray analysis resulted in an average structure of D and L, in which the chiral carbon atom appears to be flat. The pure crystals show a pyramidal shape for the chiral carbon, whereas the shape switches to almost a flat form in the structure of the solid solution crystals. However, this is only a visual observation, because the pattern of mixed crystals display the overlap of both diastereomeric structures, resulting in the flat shape. In fact, both diastereomers have a pyramidal configuration. A comparison of the D and L structures shows hardly any differences, which is inconsistent with the results of the powder diffraction.
The X-ray structure of all three complexes are depicted in Figure 4.11, Figure 4.12 and Figure 4.13.

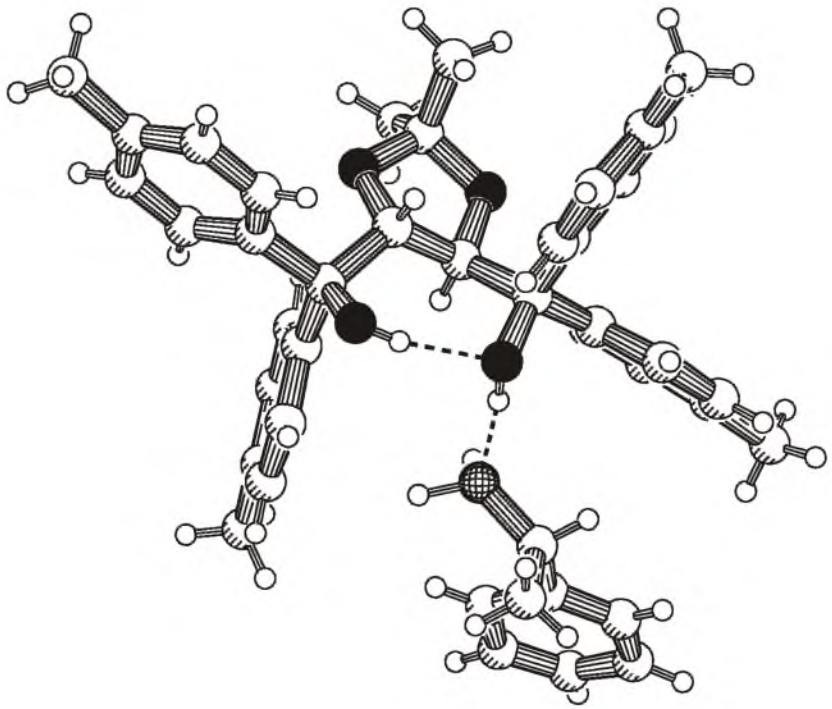


**Figure 4.11:** A PLUTON drawing of the inclusion complex of Taddol **4** and L-phenylethylamine (L)

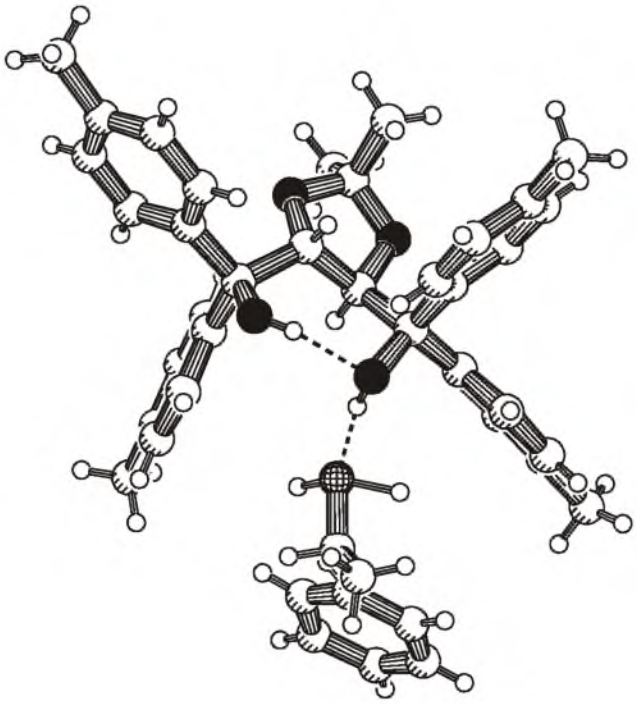


**Figure 4.12:** A PLUTON drawing of the inclusion complex of Taddol 4 and D-phenylethylamine (D)

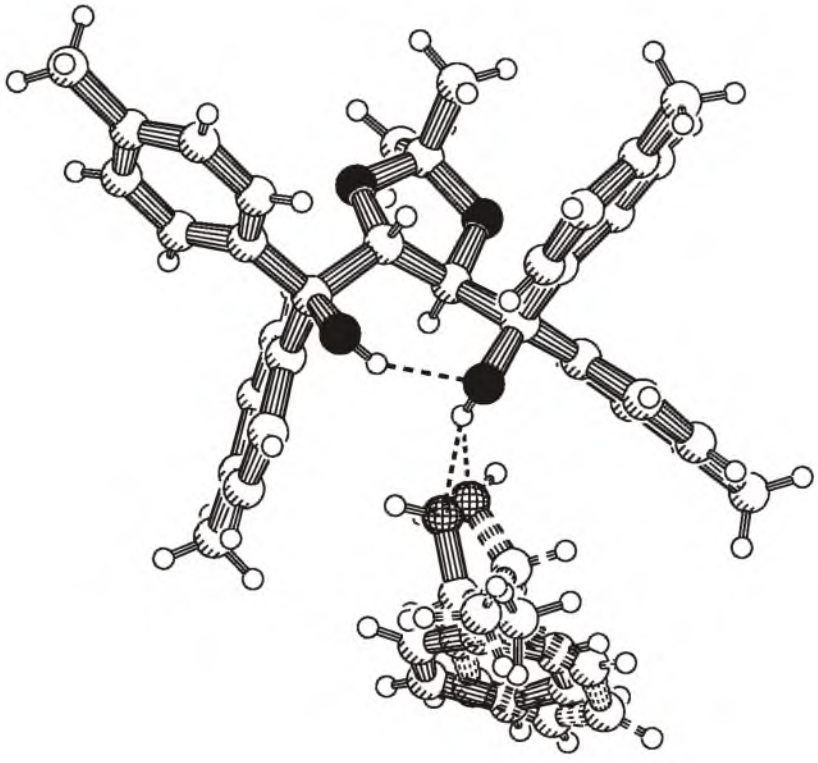


**Figure 4.13:** A PLUTON drawing of the inclusion complex of Taddol 4 and racemic phenylethylamine (DL)

## 4.7 Experimental section

For general remarks see section 2.4

*GC*
Enantiomeric excesses of phenylethylamine were determined after derivatisation with camphanic acid chloride using chiral GC (WCOT Fused Silica 25mx0.25mm, CP Chirasil-Dex CB DF 25 m, Varian).

*HPLC*
The concentration of Taddol **4** was determined by HPLC-analyses on a Shimadzu LC-10AD VP liquid chromatograph on a reverse phase column by Alltech (Econosphere, C8, 5u, 0.46 cm Ø x 25 cm).

*DSC*
DSC thermograms were recorded using a Perkin Elmer DSC7 calorimeter, calibrated with indium and acetanilide. Samples of 2mg – 8mg were weighed with an accuracy of 0.01 mg and encapsulated in aluminium pans (50μL, 0.1x2.1, Perkin Elmer). Thermograms were recorded at a scanning rate of 10°C/min under a nitrogen atmosphere. The deconvolution of peaks was performed using PeakFit 4 for Win32 (Jandel Scientific). As approximation Pearson IV peaks were used.

*Preparation of inclusion compounds*
Pure diastereomeric inclusion compounds were prepared by mixing equimolar amounts of Taddol **4** and enantiomerically pure guest compounds in heptane. The obtained crystals were re-crystallised three times from heptane. Mixed crystals were obtained by combining mixtures of guest compounds of several compositions with Taddol **4** dissolved in heptane. Enantiopure, as well as racemic, phenylethylamine is commercially available. Racemic *trans*-2-methoxycyclohexanol was synthesised [2] and resolved using Taddol **4**. Since the (*S*,*S*)-enantiomer is preferably included, the enantiomers were separated *via* inclusion resolution. The (*S*,*S*)-*trans*-2-methoxycyclohexanol was so obtained with an *e.e.* of 98 % and the (*R*,*R*)-enantiomer with an *e.e.* of 96 %.

## 4.8 Crystal structure data[12-14]

### 4.8.1 X-ray analysis of SMONA5

Crystals of SMONA5 (**L**) suitable for X-ray diffraction studies were obtained from heptane by slow evaporation of the solvent. A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Mo-Kα radiation, ω-2Θ scan mode. Unit cell dimensions were determined from the angular setting of 15 reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction (ψ-scans)[9] was applied. The structure was solved by the program CRUNCH[10] and was refined with standard methods (refinement against $F^2$ of all reflections with SHELXL97[11]) with anisotropic

parameters for the nonhydrogen atoms. The hydrogen atoms of the methyl and hydroxy groups were refined as rigid rotors to match maximum electron density in a difference Fourier map. The hydrogens attached to nitrogen were taken from a difference Fourier map. All other hydrogens were initially placed at calculated positions and were freely refined subsequently.
A structure determination summary is given in Table 4.1and a PLUTON drawing of **L** is shown in Figure 4.11.

| | |
|---|---|
| Identification code | SMONA5 |
| Crystal colour | transparent colourless |
| Crystal shape | regular fragment |
| Crystal size [mm] | 0.39 x 0.36 x 0.21 mm |
| Empirical formula | $C_{43}$ $H_{49}$ N $O_4$ |
| Formula weight | 643.83 g/mol |
| Temperature | 293(2) K |
| Radiation / Wavelength | MoK $\alpha$ (graphite mon.) / 0.71073 Å |
| Crystal system | Orthorhombic |
| Space group | $P2_12_12_1$ |
| Unit cell dimensions<br>(15 reflections 8.981<Θ<11.468) | a=12.749(6) Å, $\alpha$=90°<br>b=12.9893(14) Å, $\beta$=90°<br>c=22.418(5) Å, $\gamma$=90° |
| Volume | 3712(2) $Å^3$ |
| Calculated density | 1.152 $Mg/m^3$ |
| Z | 4 |
| Absorption coefficient | 0.073 $mm^{-1}$ |
| Diffractometer / scan | Enraf-Nonius CAD4 / $\omega$-2Θ |
| F(000) | 1384 |
| Θ range for data collection | 2.88 - 27.48° |
| Index ranges | $0 \le h \le 16$, $-16 \le k \le 0$, $-29 \le l \le 0$ |
| Reflections collected / unique | 4730 / 4730 |
| Reflections observed | 1673 ($[I_o>2\sigma(I_o)]$) |
| Absorption correction | Semi-empirical from $\psi$-scans |
| Range of relat. transm. factors | 1.053 and 0.956 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Computing | SHELXL-97 (Sheldrick, 1997) |
| Data / restraints / parameters | 4730 / 0 / 450 |
| Goodness-of-fit on $F^2$ | 1.003 |
| SHELXL-97 weight parameters | 0.027500 0.221300 |
| Final R indices [I>2σ(I)] | $R_1$ = 0.0719, $wR_2$ = 0.0878 |
| R indices (all data) | $R_1$ = 0.2404, $wR_2$ = 0.1225 |
| Largest diff. peak and hole | 0.142 and -0.141 $e.Å^{-3}$ |

**Table 4.1:** Crystal data and structure refinement for **L**

### 4.8.2 X-ray analysis of SMONA10C

Crystals of SMONA10C (**D**) suitable for X-ray diffraction studies were obtained from heptane by slow evaporation of the solvent. A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Cu-K$\alpha$ radiation, $\omega$-2$\Theta$ scan mode. Unit cell dimensions were determined from the angular setting of 15 reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction ($\psi$-scans)[9] was applied. The structure was solved by the program CRUNCH[10] and was refined with standard methods (refinement against $F^2$ of all reflections with SHELXL97[11]) with anisotropic parameters for the nonhydrogen atoms. The hydrogen atoms of the methyl and hydroxy groups and the hydrogens attached to nitrogen were refined as rigid rotors to match maximum electron density in a difference Fourier map. All other hydrogens were initially placed at calculated positions and were freely refined subsequently.
A structure determination summary is given in Table 4.2and a PLUTON drawing of **D** is shown in Figure 4.12.

| | |
|---|---|
| Identification code | SMN10C |
| Crystal colour | transparent colourless |
| Crystal shape | rough fragment |
| Crystal size [mm] | 0.32 x 0.31 x 0.25 mm |
| Empirical formula | $C_{43}$ $H_{49}$ N $O_4$ |
| Formula weight | 643.83 g/mol |
| Temperature | 293(2) K |
| Radiation / Wavelength | CuK$\alpha$ (graphite mon.) / 1.54184Å |
| Crystal system | Orthorhombic |
| Space group | $P2_12_12_1$ |
| Unit cell dimensions<br>(25 reflections 22.698<$\Theta$< 27.712) | a= 12.7808(8) Å, $\alpha$=90°<br>b= 13.0447(6) Å, $\beta$=90°<br>c= 22.5947(8) Å, $\gamma$=90° |
| Volume | 3767.0(3) $Å^3$ |
| Calculated density | 1.135Mg/$m^3$ |
| Z | 4 |
| Absorption coefficient | 0.561 $mm^{-1}$ |
| Diffractometer / scan | Enraf-Nonius CAD4 / $\omega$-2$\Theta$ |
| F(000) | 1384 |
| $\Theta$ range for data collection | 3.91- 69.86° |
| Index ranges | $0 \le h \le 15$, $0 \le k \le 15$, $0 \le l \le 27$ |
| Reflections collected / unique | 3997 / 3997 |
| Reflections observed | 2564 ([$I_o$>2$\sigma$($I_o$)]) |
| Absorption correction | Semi-empirical from $\psi$-scans |
| Range of relat. transm. factors | 1.026 and 0.972 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Computing | SHELXL-97 (Sheldrick, 1997) |
| Data / restraints / parameters | 3997 / 2 / 448 |
| Goodness-of-fit on $F^2$ | 1.024 |
| SHELXL-97 weight parameters | 0.071800 0.717600 |

| Identification code | SMN10C |
|---|---|
| Final R indices [I>2σ(I)] | $R_1$ = 0.0560, $wR_2$ = 0.1356 |
| R indices (all data) | $R_1$ = 0.0918, $wR_2$ = 0.1593 |
| Largest diff. peak and hole | 0.208 and -0.163 e.Å$^{-3}$ |

**Table 4.2:** Crystal data and structure refinement for **D**

### 4.8.3 X-ray analysis of SMONA8

Crystals of SMONA8 (**DL**) suitable for X-ray diffraction studies were obtained from heptane by slow evaporation of the solvent. A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Mo-Kα radiation, ω-2Θ scan mode. Unit cell dimensions were determined from the angular setting of 15 reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction (ψ-scans)[9] was applied. The structure was solved by the program CRUNCH[10] and was refined with standard methods (refinement against $F^2$ of all reflections with SHELXL97[11]) with anisotropic parameters for the nonhydrogen atoms. The hydrogen atoms of the methyl and hydroxy groups and the hydrogens attached to nitrogen were refined as rigid rotors to match maximum electron density in a difference Fourier map. All other hydrogens were initially placed at calculated positions and were freely refined subsequently. The crystal structure contains both the D and the L form of phenylethylamine. The structure could successfully be refined using a disorder model describing the presence of the two enantiomers.
A structure determination summary is given in Table 4.3 and a PLUTON drawing of **DL** is shown in Figure 4.13.

| Identification code | SMONA8 |
|---|---|
| Crystal colour | transparent colourless |
| Crystal shape | very rough fragment |
| Crystal size [mm] | 0.29 x 0.20 x 0.19mm |
| Empirical formula | $C_{43}$ $H_{49}$ N $O_4$ |
| Formula weight | 643.83 g/mol |
| Temperature | 293(2) K |
| Radiation / Wavelength | MoKα (graphite mon.) / 0.71073 Å |
| Crystal system | Orthorhombic |
| Space group | $P2_12_12_1$ |
| Unit cell dimensions<br>(25 reflections 8.943<Θ< 10.862) | a= 12.766(5) Å, α=90°<br>b= 13.034(3) Å, β=90°<br>c= 22.578(6) Å, γ=90° |
| Volume | 3757.0(18) Å$^3$ |
| Calculated density | 1.138 Mg/m$^3$ |
| Z | 4 |
| Absorption coefficient | 0.072 mm$^{-1}$ |
| Diffractometer / scan | Enraf-Nonius CAD4 / ω-2Θ |
| F(000) | 1384 |
| Θ range for data collection | 2.87 - 27.45° |
| Index ranges | 0 ≤ h ≤ 16, 0 ≤ k ≤ 16, 0 ≤ l ≤ 29 |

| | |
|---|---|
| Identification code | SMONA8 |
| Reflections collected / unique | 4773 / 4773 |
| Reflections observed | 1147 ($[I_o>2\sigma(I_o)]$) |
| Absorption correction | Semi-empirical from $\psi$-scans |
| Range of relat. transm. factors | 1.021 and 0.972 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Computing | SHELXL-97 (Sheldrick, 1997) |
| Data / restraints / parameters | 4730 / 0 / 450 |
| Goodness-of-fit on $F^2$ | 1.003 |
| SHELXL-97 weight parameters | 0.027500 0.221300 |
| Final R indices [$I>2\sigma(I)$] | $R_1$ = 0.0719, $wR_2$ = 0.0878 |
| R indices (all data) | $R_1$ = 0.2404, $wR_2$ = 0.1225 |
| Largest diff. peak and hole | 0.142 and -0.141 e.Å$^{-3}$ |

**Table 4.3:** Crystal data and structure refinement for **DL**

## 4.9 References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# 5 Dipeptides, suitable hosts in inclusion resolution ?

*In this chapter the inclusion capabilities of dipeptide host compounds via sorption and crystallisation are described. A diverse range of racemic compounds such as alcohols, sulfoxides and ketones have been used.*

## 5.1 Introduction

As was described in Chapter 1, *(R)*-phenylglycyl-*(R)*-phenylglycine and some derivatives are suitable for the enantioselective preparation of inclusion complexes. Akazome[1,2,3,5,6,11] extensively studied a limited number of these dipeptides, and in these experiments it was shown that they have promising capabilities for the resolution of neutral, chiral molecules.
The prospect of obtaining a series of new resolving agents, derived from readily available materials, allowing a considerable structural variation and which have not been investigated in inclusion complexation before, was a strong impetus to a further study of dipeptide hosts and to compare their capabilities as resolving agents to the Taddols (see chapter 2.3). Information about the suitability of inclusion resolution with dipeptide hosts for an industrial application will so be collected.
*Akazome* and co-workers reported a number of successful compounds derived from phenylglycine for the use in inclusion resolution. With these agents, procedures to successfully separate enantiomers in high *e.e.*'s and good yields have been developed.
In this chapter, the attempts to prepare inclusion complexes with twelve different dipeptides based on phenylglycine as potential host molecules and a large selection of guest compounds using two different techniques are described.

## 5.2 Synthesis of potential dipeptide host compounds

The dipeptides **1**-**4** derived from phenylglycine were synthesised to investigate their inclusion capabilities and to extend the search for separations of racemates *via* inclusion complexation. Compound **1** is already known and has been described in the literature before.[6]

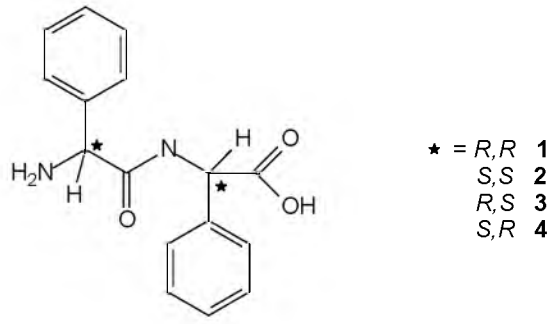
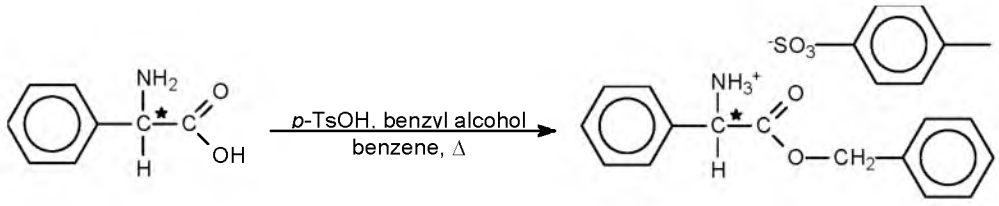



**Figure 5.1:** 4 phenylglycine dipeptides

The synthesis of these four dipeptides was time consuming, because re-crystallisation after each reaction step is required to obtain the compounds sufficiently pure for further reactions. Starting from optically pure phenylglycine, four reaction steps are needed to prepare the dipeptides. Before coupling two peptides (or amino acids), the amino group of one peptide as well as the carboxylic group of the other were protected.

For the protection of the carboxylic group of (*R*)- and (*S*)-phenylglycine, the benzyl esters were prepared as the *p*-toluene sulfonate salts in 87% (**5**) and 85% (**6**) yield after re-crystallisation.

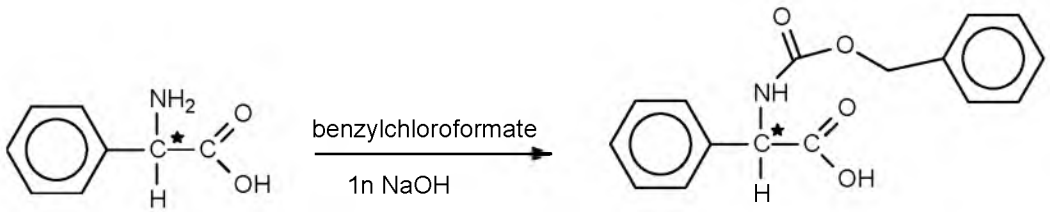



phenylglycine

[2-(benzyloxy)-2-oxo-1-phenylethyl]ammonium 4-methyl-1-benzenesulfonate ★ = *R* **5**, *S* **6**

**Scheme 5.1:** Synthesis of the benzyl ester p-toluene sulfonates of (*R*)-phenylglycine **5** and (*S*)-phenylglycine **6**

The amino groups of (*R*)- and (*S*)-phenylglycine were protected by a BOC group in 85% (**7**) and 82% (**8**) yield after re-crystallisation.

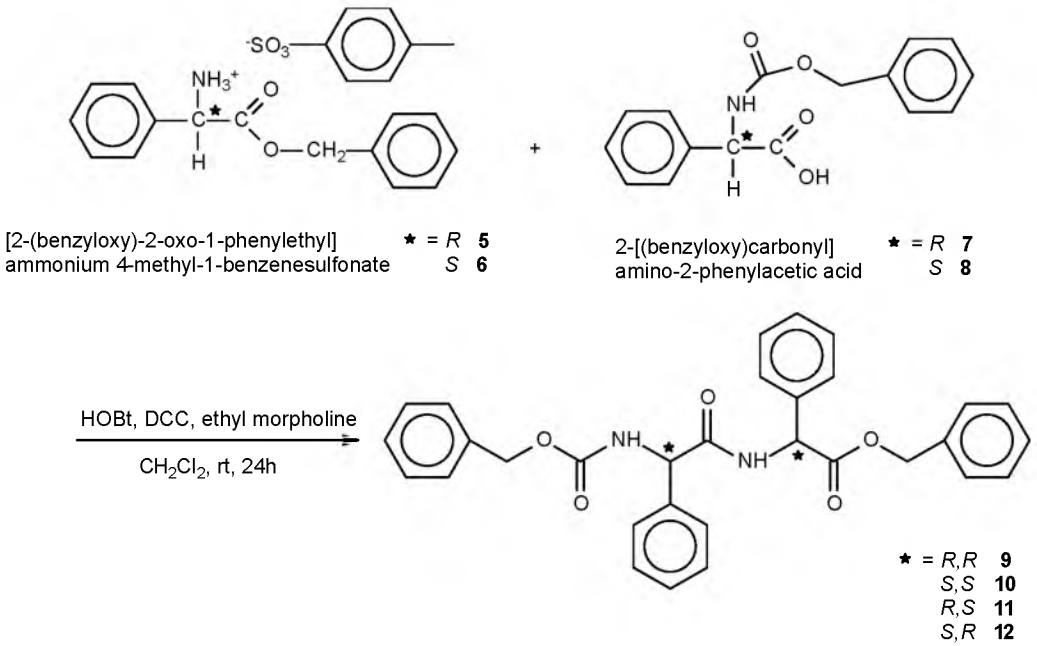



phenylglycine

2-[(benzyloxy)carbonyl] amino-2-phenylacetic acid ★ = *R* **7**, *S* **8**

**Scheme 5.2:** Synthesis of the N-benzyloxycarbonyl phenylglycines of **7** and **8**

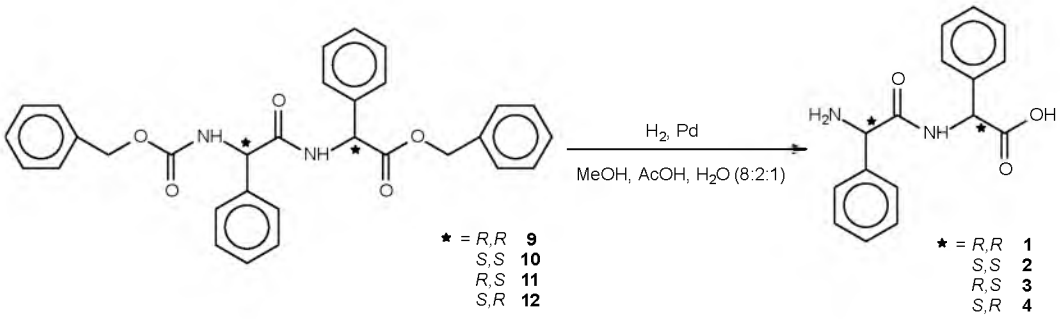
Using to the DCC-HOBt coupling method, the [2-(benzyloxy)-2-oxo-1(*S*)-phenylethyl] ammonium 4-methyl-1-benzenesulfonates (**5**, **6**) and the 2-[(benzyloxy)carbonyl] amino-2-phenylacetic acids (**7**, **8**) gave the protected dipeptides **9**-**12**.




**Scheme 5.3:** Peptide coupling

The first attempts of coupling according to the literature[4] indeed resulted in the dipeptides, but impure and in low yields. An extension of the reaction time and a change in the order of addition of the reactants improved both yield and purity. Despite this, a suitable crystallisation method was also needed to purify the dipeptides further before deprotection. A mixture of EtOAc and heptane was used for the crystallisation leading to sufficiently pure products. However, removal of remaining traces of heptane was cumbersome.

A hydrogenation with palladium as catalyst is the final step.




**Scheme 5.4:** Deprotection to obtain phenylglycyl-phenylglycines **1**-**4**

Re-crystallisation of the crude hydrogenation products gave the four dipeptides **1**-**4**.

*Conclusion:*

In summary, eight different possible host compounds **1**-**4** and **9**-**12** have been synthesised. In general, their syntheses were facile, only the purification presented some problems. For an application of these compounds in inclusion resolution, their purity is essential, since inclusion crystallisation has to deal with the problem of nucleation as well (see section 3.3.1). Purification by crystallisation was laborious, and the removal of the solvent also took time. It should be noted, however that the tendency to include solvents shows promise for other inclusions.

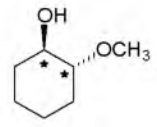
These dipeptides represent possible host compounds, and, because of their small differences in molecular structure, the inclusion capabilities and required experimental conditions can be investigated in detail.

## 5.3 Guest compounds

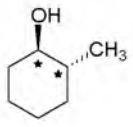
The guest compounds to be included in the dipeptide hosts should, in analogy with those which can be included in Taddol host compounds, fulfil certain criteria, as as is revealed by an analysis of the literature examples.[2,3,5-8,11] All guests mentioned in literature so far are relatively small compounds and contain functional groups, suitable for hydrogen bonding with the hosts. The guest compound should not contain an acid or amino function, in order to prevent salt formation. These criteria have played a major role in the selection of the guest used in the present study. Most of the molecules selected are small and contain at least one functional group, such as an alcohol or a sulfoxide. Moreover, the industrial relevance of the guest molecules was a factor in selecting them. Many of them are precursors for pharmaceuticals or other fine chemicals. The majority of guest compounds is readily available as racemates and many are difficult to resolve. The two possible guest compounds, **R33** and **R34** are not chiral, they were used in an investigation on the influence of the sulfonyl oxygens.

The guest compounds are collected in Table 5.1.

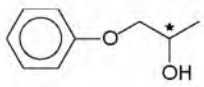
**Alcohols**



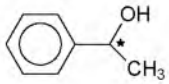

**R8**



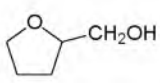

**R9**



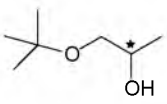

**R11**



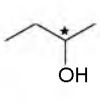

**R12**



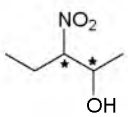

**R13**



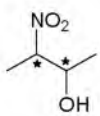

**R14**



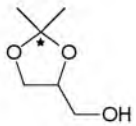

**R15**



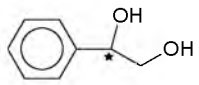

**R18**



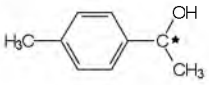

**R19**




**R23**

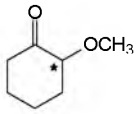



R24

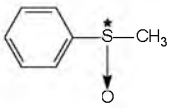



R35

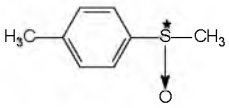
**Miscellaneous**



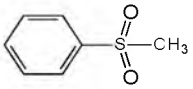

R27



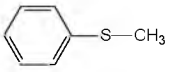

R31




R32




R33



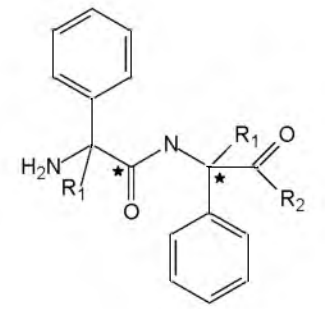

R34

**Table 5.1:** Guest compounds used in inclusion experiments with dipeptide hosts

## 5.4 Inclusion experiments

According to the lead literature[6] about dipeptide inclusion resolution by Akazome and co-workers, two different techniques, crystallisation and sorption were applied to obtain inclusion complexes.

In addition to the eight dipeptides mentioned above, four dipeptides provided by the University of Padova, Italy, have also been tested for their inclusion behaviour. These peptides are derived from $\alpha$–methyl phenylglycine. The extra methyl group blocks possible racemisation of the peptide units during resolution or work-up. However, the possibility for asymmetric transformation of the guest compound through *in situ* racemisation is also hampered.




$R_1 = CH_3$ $R_2 = OH$
★ *S,S* **13**
*S,R* **14**

$R_1 = CH_3$ $R_2 = NH_2$
★ *R,R* **15**
*S,R* **16**

**Figure 5.2:** Dipeptides derived from $\alpha$–methyl phenylglycine

### 5.4.1 Crystallisation

All 12 dipeptides derived from phenylglycine were tested for their inclusion capabilities with 17 selected guests.

The experiments were performed with a host/guest *ratio* of 1:2 in water at pH 6.5 at room temperature.[5]

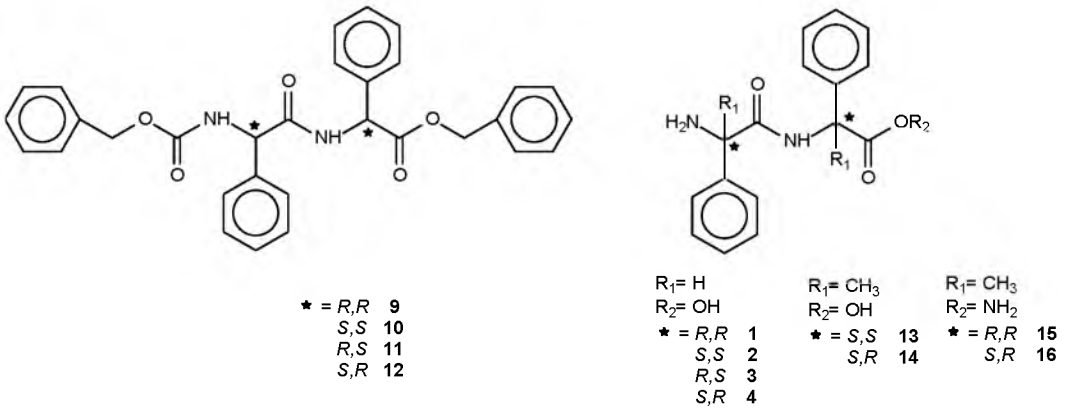



**Figure 5.3:** Twelve dipeptides based on phenylglycine

In Table 5.2 204 crystallisations from solution experiments are summarised.

| guest compounds | | host compound | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **1** | **2** | **3** | **4** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** |
| R8 | *trans*-2-methoxycyclohexanol | – | ○ | ○ | ○ | – | ○ | – | – | – | ○ | ○ | ○ |
| R27 | 2-methylcyclohexanone | – | – | ○ | ○ | – | – | – | – | – | ○ | ○ | ○ |
| R9 | *trans*-2-methylcyclohexanol | – | – | – | ○ | – | – | – | – | ○ | ○ | – | ○ |
| R23 | solketal | ○ | ○ | ○ | ○ | – | – | – | – | – | ○ | – | – |
| R19 | 3-nitro-2-butanol | – | – | ○ | – | – | – | – | – | – | ○ | – | – |
| R18 | 3-nitro-2-pentanol | – | – | ○ | – | ○ | – | – | – | – | ○ | ○ | – |
| R15 | *sec*-butanol | – | ○ | ○ | ○ | – | ○ | ○ | – | ○ | ○ | ○ | ○ |
| R12 | phenethylalcohol | ○ | ○ | ○ | ○ | – | – | – | – | ○ | ○ | ○ | ○ |
| R35 | *p*-tolylethylalcohol | – | ○ | – | ○ | – | – | – | – | – | ○ | – | ○ |
| R13 | tetrahydrofurfuryl alcohol | – | – | – | – | – | – | – | – | – | – | – | – |
| R11 | 1-phenoxy-2-propanol | – | – | – | ○ | – | – | – | – | – | ○ | ○ | ○ |
| R14 | 1-*tert*-butoxy-2-propanol | ○ | ○ | – | ○ | – | – | – | – | – | ○ | ○ | ○ |
| R23 | 1-phenyl-1,2-ethanediol | ○ | ○ | ○ | ○ | – | – | – | – | ○ | ○ | – | – |
| R31 | methyl phenyl sulfoxide | 90 ee* | ○ | ○ | ○ | – | – | – | – | – | ○ | ○ | ○ |
| R32 | methyl *p*-tolyl sulfoxide | ○ | ○ | ○ | ○ | – | – | – | – | ○ | ○ | ○ | ○ |
| R33 | methyl phenyl sulfide | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | – | – | ○ | ○ |
| R34 | thioanisole | ○ | – | – | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

– no inclusion ○ no crystals * resolution already described in literature[5]

**Table 5.2:** Crystallisation experiments

In order to gain some experience in using the dipeptides in inclusion experiments, a literature experiment described by Akazome[5,6] was first reproduced (see Table 5.2, R31). Akazome *et al*. observed resolution of methyl phenyl sulfoxide with a high *(R)*-enantioselectivity (92-93% *e.e.*) in an inclusion complex with dipeptide **1**. (*R*)-phenylglycyl-(*R*)-phenylglycine **1** was crystallised in the presence of racemic methyl phenyl sulfoxide. (*R*)-sulfoxide was included with an *e.e.* of 93% after several days. Repeating this experiment gave an *e.e.* of 90%.

The crystals obtained were dissolved and analysed by $^1$H-NMR, GC or HPLC.

Unfortunately, no new inclusion complexes have been obtained in the crystallisation experiments with the dipeptides; only the repetition of the literature example was successful. The sulfoxide group, and therewith the possibility of hydrogen-bond formation, is apparently of essential importance, since an inclusion with the guests **R33** and **R34** in dipeptide **1** did not occur. The sulfoxide **R31** is accommodated in a void between the layers formed by self-assembled dipeptide **1** *via* the alternating salt formation between $NH_2$ and COOH to form a sheet. They can interact at three different points: hydrogen-bonding between $NH_3^+$ and the sulfinyl group, aromatic interaction and the CH/$\pi$ interaction of the phenyl and alkyl groups. The first mentioned interaction must be the one that is most responsible for a successful inclusion. Racemic guest **R32**, *p*-tolyl methyl sulfoxide, does possess a sulfinyl group for hydrogen-bonding, but the extra $CH_3$-group in the *para*-position of the aromatic part seems to be too large to fit into the void formed by the phenyl groups located perpendicular to the layer, stacking in an edge-to-face fashion.

The formation of inclusion complexes requires a higher stability and lower solubility of these complexes compared to the individual components. Obviously, these conditions were not fulfilled in almost all attempted cases. However, in many experiments described in Table 5.2 obtaining the first crystalline material (nucleation) will also limit the rate of success. Compound **13** tends to include water and therefore only this water-inclusion complex crystallises in all experiments with **13**.

### 5.4.2 Sorption

An alternative method to prepare inclusion compounds is direct sorption of the guest into the crystalline host compound (see section 2.2.2). A slurry of the crystalline dipeptides and the dissolved racemic guest compounds were stirred together in heptane at room temperature with a host/guest ratio of 1:2. After two days the solid was filtered off, washed and dissolved in water at pH 6.5. The guest compound was extracted with methylene chloride and water, and the organic layer was analysed.

| guest compound | | host compound | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **1** | **2** | **3** | **4** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** |
| R8 | *trans*-2-methoxycyclohexanol | – | – | – | – | – | – | – | – | – | – | – | – |
| R27 | 2-methylcyclohexanone | – | – | – | – | – | – | – | – | – | – | – | – |
| R9 | *trans*-2-methylcyclohexanol | – | – | – | – | – | – | – | – | – | – | – | – |
| R23 | solketal | – | – | – | – | – | – | – | – | 48*ee* | – | – | – |
| R19 | 3-nitro-2-butanol | – | – | – | – | – | – | – | – | – | – | – | – |
| R18 | 3-nitro-2-pentanol | – | – | – | – | – | – | – | – | – | – | – | – |
| R15 | *sec*-butanol | – | – | – | – | – | – | – | – | – | – | – | – |
| R12 | phenethylalcohol | – | – | – | – | – | – | – | – | – | – | – | – |
| R35 | *p*-tolylethylalcohol | – | – | – | – | – | – | – | – | – | – | – | – |
| R13 | tetrahydrofurfuryl alcohol | – | – | – | – | – | – | – | – | – | – | – | – |
| R11 | 1-phenoxy-2-propanol | – | – | – | – | – | – | – | – | – | – | – | – |
| R14 | 1-*tert*-butoxy-2-propanol | – | – | – | – | – | – | – | – | – | – | – | – |
| R24 | 1-phenyl-1,2-ethanediol | – | – | – | – | – | – | – | – | – | – | – | – |
| R31 | methyl phenyl sulfoxide | 91*ee** | 73*ee* | – | – | – | – | – | – | 36*ee* | – | – | – |
| R32 | methyl *p*-tolyl sulfoxide | – | – | – | – | – | – | – | – | – | – | – | – |
| R33 | methyl phenyl sulfide | – | – | – | – | – | – | – | – | – | – | – | – |
| R34 | thioanisole | – | – | – | – | – | – | – | – | – | – | – | – |

– no inclusion  * resolution already described in literature[7,8]

**Table 5.3:** Sorption experiments

In order to gain some experience in using the dipeptides in inclusion experiments, again a literature experiment described by Akazome[7,8] *et al.* was first reproduced (see Table 5.3, R31). Akazome observed resolution of methyl phenyl sulfoxide with a high *(R)*-enantioselectivity (92-93% *e.e.*) in an inclusion complex with dipeptide **1**. (*R*)-phenylglycyl-(*R*)-phenylglycine **1** was stirred in the presence of racemic methyl phenyl sulfoxide.

(*R*)-sulfoxide was included with an *e.e.* of 92% after several days. Repetition of this experiment afforded an *e.e.* of 91%. However, the experiment in which (*S*)-phenylglycyl-(*S*)-phenylglycine **2** was stirred in the presence of racemic methyl phenyl sulfoxide afforded the (*S*)-sulfoxide with an *e.e.* of 73%. The difference between the antipodal hosts is circumstancial.

The solids obtained were dissolved and analysed by GC or HPLC. Two new inclusion complexes were formed applying the sorption method. Dipeptide **13** is also able to resolve methyl phenyl sulfoxide, affording an *e.e.* of 36%. In addition, solketal, is resolved with **13**, affording an *e.e.* of 48%. Since the latter inclusion complex is the most promising new one found, it was analysed in more detail as will be described in the next section.

Since the resolution of methyl phenyl sulfoxide by host **1** is the lead example for the present inclusion experiments with dipeptide hosts, thioanisole and phenyl methyl sulfone have been additionally used as guest compounds as well in order to investigate the influence of the

hydrogen bonding in the formation of inclusion. The inclusion crystals of **1** with methyl phenyl sulfoxide have a hydrogen-bound network of the dipeptide molecules to construct a layer. The sulfoxide molecules are in the channel between the walls of the dipeptide phenyl groups, which are perpendicular to the layer. The central amino proton of the channel binds to the sulfinyl oxygen, and the aromatic groups create a cavity. A lack of oxygen or an extra one seems to have a negative influence on the formation of inclusion crystals. No inclusion crystals with these two new guest compounds were obtained *via* sorption, confirming the results obtained by the crystallisation method.

### 5.4.3 Dipeptide 13 and solketal

Different attempts were made to obtain inclusion crystals of **13** and solketal *via* crystallisation and sorption. It was observed that solketal was resolved by **13** *via* sorption, but not *via* crystallisation. This surprising result was a reason to perform a number of additional experiments. Sorption experiments were performed with different solvents and in different host/guest ratios. The results are collected in Table 5.4.

| entry | host:guest | solvent | *e.e.*% |
|---|---|---|---|
| 1 | 1:2 | hexane | 48 |
| 2 | 1:2 | methanol | 33 |
| 3 | 1:2 | water,pH 6.5 | 0 |
| 4 | 1:10 | hexane | 45 |
| 5 | 1:10 | methanol | 30 |
| 6 | 1:10 | water, pH 6.5 | 2 |

**Table 5.4:** Sorption experiments with **13** and *rac.* solketal

Inclusion was observed in all 6 cases. The best results were obtained using hexane as solvent. The low solubility in hexane of both, host and guest may be a governing factor. The host/guest ratio seems not to be of great importance.
Crystallisation experiments in methanol or without solvent and with solketal itself as a solvent have also been performed at different temperatures and in different host/guest ratios. Table 5.5 shows the results.

| entry | host:guest | temperature | product | *e.e.*% |
|---|---|---|---|---|
| 7 | 1:2 | rt | host-hydrate | - |
| 8 | 1:2 | -20°C | host-hydrate | - |
| 9 | 1:10 | rt | host-hydrate | - |
| 10 | 1:10 | -20°C | host-hydrate | - |
| 11 | 1: solketal as solvent | rt | host-solketal 1:1 | 0 |
| 12 | 1: solketal as solvent | -20°C | host-solketal 1:1 | 0 |

**Table 5.5:** Crystallisation experiments with **13** and *rac.* solketal

Crystals were obtained in all six cases. The crystals obtained in entries 7 to 10 are colourless and no longer soluble in methanol, whereas the pure host does dissolve in methanol. X-ray analysis and $^1$H-NMR proved the colourless crystals to be inclusion crystals of **13** with water without solketal, similar to the results summarised in
Table 5.2. An additional crystallisation attempt analogous to entry 7 was therefore performed in water-free methanol. A 1:1 inclusion complex of **13** and *rac.* solketal was obtained where the *e.e.* of solketal was zero.
Entries 11 and 12, in which solketal was used as the solvent, both afforded 1:1 inclusion complexes of **13** and rac. solketal where the *e.e.* of solketal was also zero. Since it is possible to obtain an inclusion complex *via* crystallisation without an additional solvent, attempts were made to produce inclusion crystals with *(R)*-solketal and *(S)*-solketal, respectively.

| entry | host:guest | temperature | inclusion |
|---|---|---|---|
| 13 | 1: (*R*)-solketal as solvent | rt | yes |
| 14 | 1: (*S*)- solketal as solvent | rt | yes |

**Table 5.6:** Crystallisation experiments with **13** and enantiopure solketal

The data in Table 5.6 show that both, (*R*)- and *(S)*-solketal can form an 1:1 complex with dipeptide **13** *via* crystallisation.
A comparison of these crystals by X-ray powder diffraction resulted in a different spectrum for each diastereomeric inclusion complex, as expected (Diagram 5.1).

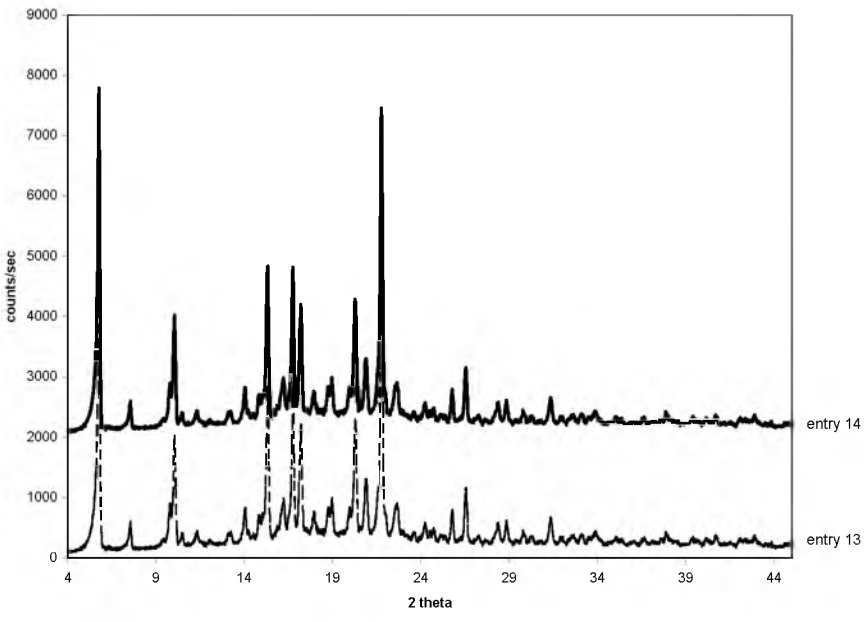



**Diagram 5.1:** XRPD spectra of entry 13 and entry 14

The diastereomeric inclusion complexes of dipeptide **13** and the enantiomers of solketal show significant differences in their powder diffraction spectra, therefore one can conclude that they crystallise in different crystal structures. The crystals obtained in entry 11 (crystallisation experiment with racemic solketal as solvent) were therefore analysed by XRPD and compared to the powder diffraction spectra of the pure dipeptide and the sorption crystals (entry 4). The pure dipeptide is amorphous, therefore no clear signals are present in its powder diffraction spectrum. The 1:1 inclusion complex of **13** and solketal (entry 11) shows a different X-ray powder spectrum compared to the material of the sorption experiment (entry 4). The large difference between crystallisation from solution and from inclusion by sorption (Diagram 5.2) can only be explained by different crystal forms (polymorphism). This also explains the difference in enantioselectivity between crystallisation and sorption. Only the polymorph obtained *via* sorption shows some enantioselectivity.

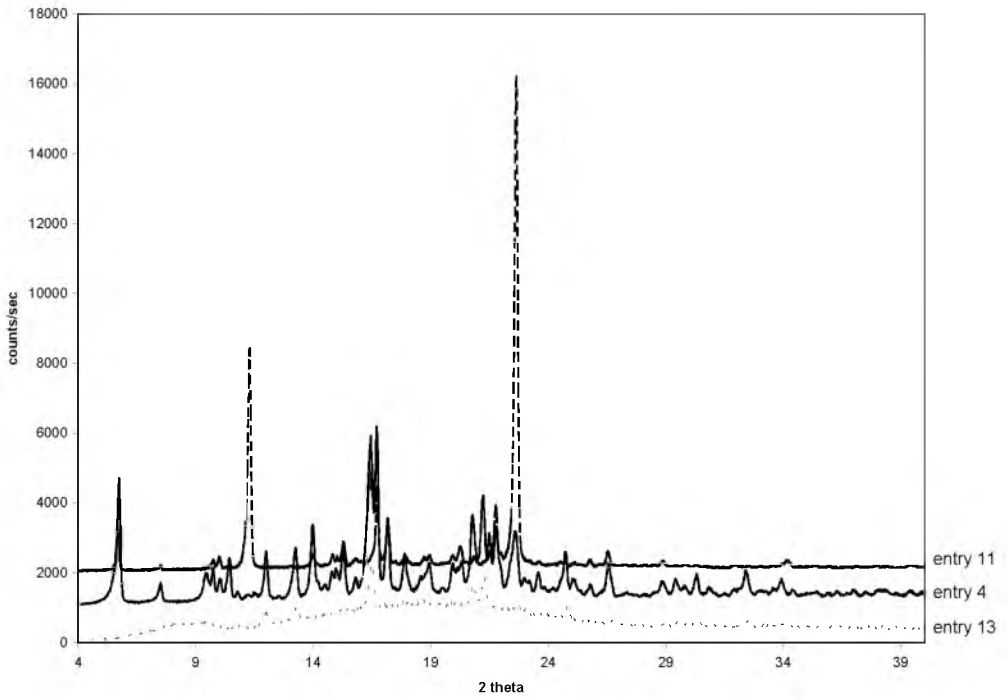
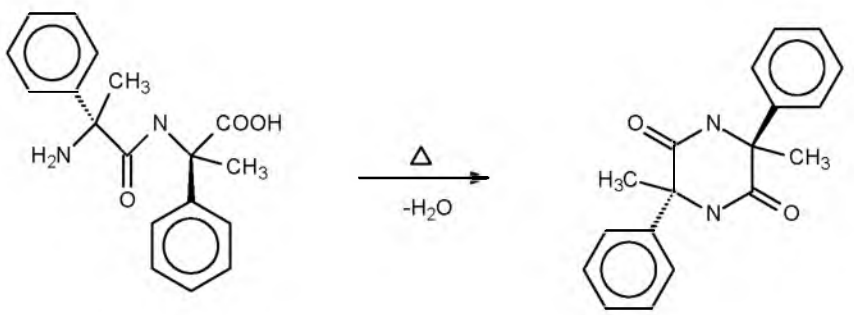



**Diagram 5.2:** XRPD- spectra

Final proof for the presence of polymorphs was obtained by using induced crystallisation from solution. A solution of dipeptide **13** was prepared in racemic solketal. After cooling, the clear solution was seeded with pure dipeptide. This does not dissolve, but forms sorption-type crystals which act as templates for further crystallisation. The inclusion complex formed was analysed, and an *e.e.* of the *(R)*-solketal of 33% was measured, a value that is similar to the sorption experiments.

Another example of polymorphism was found in literature studies[3] of Akazome's inclusion complexes with dipeptides. He found, that dipeptides tend to self-assemble into various structures, and dipeptide **1** for example forms channel-type or pocket-type cavities with its phenyl-groups for the inclusion of guest molecules, depending on the respective guest compound. Unfortunately, the inclusion crystals obtained from dipeptide **13** and solketal are not suitable for single crystal X-ray analysis to evaluate the detailed structures.
An attempt was made to include solketal *via* the distillation method, but the dipeptide **13** condenses to the diketopiperazine **17** and sublimes upon heating.




**13** **17**

**Scheme 5.5:** Condensation of **13** to **17**

## 5.5 Conclusions

Based on the lead example provided by Akazome, simple dipeptides were expected to serve as hosts for many inclusion resolutions. Unfortunately, the inclusion of methyl phenyl sulfoxide as found by Akazome turned out to be an exception, a so-called lucky hit. In the present research, only one additional compound has been identified to form an inclusion complex with dipeptide hosts. However, the resolution of this compound, solketal, was complicated by the formation of polymorphic crystal forms.
Given the large number of peptides available and the increasing insight into their crystallisation and conformational behaviour, it will be worthwhile to continue research for new inclusion complexes in this direction. On the other hand, however, the desire to develop a new industrially viable resolution method has not been fulfilled. Given the limited number of additional successful examples as shown in this thesis and the difficulties in reproducing literature examples, it is safe to conclude that inclusion resolutions have a rather limited scope for larger scale applications. For crystal and molecular studies, the phenomenon can be attractive for further work. In fact, this will certainly be needed, since also the desire to develop more rationality and design in resolution of racemates has not come closer to reality. One might even conclude that inclusion resolutions, in which interactions in crystal

forming are governed by an intricate interplay of weak forces (compared to i.e. ionic forces in diastereomer salt resolutions), are even more depending on a "trial and error" approach than resolutions through diastereomeric salts.

## 5.6 Experimental section

For *General Remarks* see Chapter 2.

*General procedure **A**: [2-(benzyloxy)-2-oxo-1-phenylethyl]ammonium 4-methyl-1-benzene sulfonate* [9]
0.25 mol phenylglycine, 0.25 mol p-toluene sulfonic acid monohydrate, 100 ml benzyl alcohol and 50 ml benzene were placed in a 500 ml round-bottomed flask fitted with a soxhlet extractor filled with molsieves (4Å) and heated under reflux. After 5 h the reaction mixture was cooled to room temperature and 250 ml benzene and 400 ml dry ether were added. The crystalline salt was filtered off after standing for 2 h at 4°C, washed with dry ether and re-crystallised from methanol-ether.

*General procedure **B**: 2-[(benzyloxy)carbonyl]amino-2-phenylacetic acid* [10]
Benzyl chloroformate (0.15 mol) and 1N-sodium hydroxide were simultaneously added dropwise during 45 min to a stirred solution of phenylgycine (0.15 mol) in 146 ml 1N-sodium hydroxide at 0°C, the rates of adding being such as to keep the mixture at pH 8-9. After addition the solution was stirred at pH 8 for 30 min at 0°C, then warmed to room temperature. It was washed twice with 150 ml ether. It was again cooled to 0°C and added slowly with stirring to ice-cold 5N-hydrochloric acid (15 ml). The solid was filtered off, washed with water, dried *in vacuo* and re-crystallised from water/ethanol.

*General procedure **C**: Coupling*[4]
To a suspension of 10 mmol N-(benzyloxycarbonyl)phenylglycine and 10 mmol 1-hydroxy-benzotriazole in $CH_2Cl_2$ at 0°C, 11 mmol dicyclohexylcarbodiimide is added and the reaction is stirred for 1 h at this temperature and 1 h at room temperature. Then 10 mmol N-ethyl morpholine and 10 mmol phenylglycine benzyl ester p-toluene sulfonate were added and the reaction mixture was stirred for one more hour. The solid was filtered off and the solvent was evaporated. The residue was dissolved in EtOAc, washed with saturated $NaHCO_3$ solution, 2N citric acid, saturated $NaHCO_3$ solution and water. After drying over $Na_2SO_4$, the solvent was evaporated and the solid crystallised from EtOAc/hexane.

*General procedure **D**: Deprotection*[11]
16.7 mmol of the protected dipeptide was dissolved in a mixture of 80 ml MeOH, 20 ml AcOH and 10 ml water and treated with hydrogen in the presence of Pd black (4.5g 10% Pd on C) overnight. The catalyst was removed by filtration and concentration of the filtrate gave a solid. This was dissolved in 0.2 M aqueous HCl; the pH was adjusted to about 6.5 by addition of 5 M aqueous NaOH. The solution was concentrated until a small amount of solid was deposited. Then the solution was stored in the refrigerator until a white solid was formed. It was filtered off, washed with water and dried *in vacuo*.

*[2-(benzyloxy)-2-oxo-1(R)-phenylethyl]ammonium 4-methyl-1-benzenesulfonate* **5**[11]

Procedure **A**: 37.8 g *(R)*-Phenylglycine
48.5 g TsOH

The yield was 89.82 g (87%) after re-crystallisation. Mp: 192°C; $[\alpha]_D^{20}$ = -2.0 (c0.5, EtOH); $^1$H-NMR (100 MHz, $CDCl_3$): δ 8.67 (br,3H, $-NH_3^+$), δ 7.45-7.02 (m, 14H, arom.), δ 6.02 (s, 2H, $-CH_2$), δ 4.89 (s, 1H, -CH), δ 2.24 (s,3H, $-CH_3$)

*[2-(benzyloxy)-2-oxo-1(S)-phenylethyl]ammonium 4-methyl-1-benzenesulfonate* ***6***

Procedure **A**: 37.8 g *(S)*-Phenylglycine
48.5 g TsOH

The yield was 87.75 g (85%) after re-crystallisation. Mp: 184°C; $[\alpha]_D^{20}$ = +2.0 (c0.5, EtOH); $^1$H-NMR (100 MHz, $CDCl_3$): δ 8.62 (br,3H, $-NH_3^+$), δ 7.47-7.00 (m, 14H, arom.), δ 5.98 (s, 2H, $-CH_2$), δ 4.88 (s, 1H, -CH), δ 2.26 (s,3H, $-CH_3$)

*2-[(benzyloxy)carbonyl]amino-2(R)-phenylacetic acid* ***7***[11]

Procedure **B**: 25 g Benzyl chloroformate
22 g *(R)*-Phenylglycine

The yield was 35.29 g (85%) after re-crystallisation. Mp: 131°C; $[\alpha]_D^{20}$ = -110 (c0.6, EtOH); $^1$H-NMR (100 MHz, $CDCl_3$): δ 7.44-7.38 (m, 10H, arom.), δ 5.15 (s, 1H, -CH), δ 4.95 (s, 1H, $-CH_2$)

*2-[(benzyloxy)carbonyl]amino-2(S)-phenylacetic acid* ***8***

Procedure **B**: 25 g Benzyl chloroformate
22 g *(S)*-Phenylglycine

The yield was 34.04 g (82%) after re-crystallisation. Mp: 131°C; $[\alpha]_D^{20}$ = -110 (c0.6, EtOH); $^1$H-NMR (100 MHz, $CDCl_3$): δ 7.40-7.35 (m, 10H, arom.), δ 5.12 (s, 1H, -CH), δ 4.91 (s, 1H, $-CH_2$)

*Benzyl 2-[(2-[(benzyloxy)carbonyl]amino-2-(R)-phenylacetyl)amino]-2-(R)- phenylacetate* ***9***[11]

Procedure **C**: 4.14 g **5**, 2.84 g **7**

The yield was 3.20 g (63%) after re-crystallisation. Mp: 192°C; $[\alpha]_D^{20}$ = -91 (c2, $CHCl_3$); $^1$H-NMR (100 MHz, $CD_3OD$): δ 7.41-7.09 (m, 20H, arom.); δ 5.38 (s, 1H, -CH); δ 5.36 (s, 1H, -CH); δ 4.99 (s, 4H, $-CH_2$)

*Benzyl 2-[(2-[(benzyloxy)carbonyl]amino-2-(S)-phenylacetyl)amino]-2-(S)-phenylacetate* ***10***

Procedure **C**: 4.14 g **6**, 2.84 g **8**

The yield was 3.00 g (59%) after re-crystallisation. Mp: 191°C; $[\alpha]_D^{20}$ = +89 (c2, $CHCl_3$); $^1$H-NMR (100 MHz, $CD_3OD$): δ 7.35-7.02 (m, 20H, arom.); δ 5.35 (s, 1H, -CH); δ 5.32 (s, 1H, -CH); δ 4.97 (s, 4H, $-CH_2$)

*Benzyl 2-[(2-[(benzyloxy)carbonyl]amino-2-(R)-phenylacetyl)amino]-2-(S)- phenylacetate* ***11***

Procedure **C**: 4.14 g **5**, 2.84 g **8**

The yield was 3.35 g (66%) after re-crystallisation. Mp: 162°C; $[\alpha]_D^{20}$ = +51 (c1, $CHCl_3$); $^1$H-NMR (100 MHz, $CD_3OD$): δ 7.40-7.08 (m, 20H, arom.); δ 5.38 (s, 1H, -CH); δ 5.35 (s, 1H, -CH); δ 4.97 (s, 4H, $-CH_2$)

*Benzyl 2-[(2-[(benzyloxy)carbonyl]amino-2-(S)-phenylacetyl)amino]-2-(R)- phenylacetate **9***

Procedure **C**: 4.14 g **6**, 2.84 g **7**

The yield was 2.95 g (63%) after re-crystallisation. Mp: 163°C; $[\alpha]_D^{20}$ = -49 (c1, $CHCl_3$); $^1$H-NMR (100 MHz, $CD_3OD$): $\delta$ 7.41-7.12 (m, 20H, arom.); $\delta$ 5.39 (s, 1H, -CH); $\delta$ 5.35 (s, 1H, -CH); $\delta$ 5.01 (s, 4H, $-CH_2$)

*2-[(2-amino-2(R)-phenylacetyl)amino]-2(R)-phenylacetic acid **1***[11]

Procedure **D**: 8.47 g **9**

The yield was 1.66 g (35%) after crystallisation. $[\alpha]_D^{20}$ = -62 (c0.5, MeOH); $^1$H-NMR (100 MHz, $CD_3OD$): $\delta$ 7.33 (s, 5H, arom.); $\delta$ 7.09 (s, 5H, arom.); $\delta$ 5.15 (s, 1H, -C<u>H</u>$NH_2$); $\delta$ 5.00 (s, 1H, -C<u>H</u>NH); IR: $\nu$ 3371 cm$^{-1}$, $\nu$ 3033 cm$^{-1}$, $\nu$ 1693 cm$^{-1}$, $\nu$ 1587 cm$^{-1}$

*2-[(2-amino-2(S)-phenylacetyl)amino]-2(S)-phenylacetic acid **2***

Procedure **D**: 8.47 g **10**

The yield was 1.71 g (36%) after crystallisation. $[\alpha]_D^{20}$ = +65 (c0.5, MeOH); $^1$H-NMR (100 MHz, $CD_3OD$): $\delta$ 7.31 (s, 5H, arom.); $\delta$ 7.10 (s, 5H, arom.); $\delta$ 5.13 (s, 1H, -C<u>H</u>$NH_2$); $\delta$ 5.01 (s, 1H, -C<u>H</u>NH); IR: $\nu$ 3369 cm$^{-1}$, $\nu$ 3033 cm$^{-1}$, $\nu$ 1685 cm$^{-1}$, $\nu$ 1585 cm$^{-1}$; Elemental analysis for $C_{16}H_{16}N_2O_3$: calc.C 67.59%, H 5.67%, N 9.85% found C 65.25%, H 5.67%; N 9.56; MS: ($\frac{m}{z}$) 285 ($M^+$)

*2-[(2-amino-2(R)-phenylacetyl)amino]-2(S)-phenylacetic acid **3***[12]

Procedure **D**: 8.47 g **11**

The yield was 1.94 g (41%) after crystallisation. $[\alpha]_D^{20}$ = +22 (c0.3, MeOH); $^1$H-NMR (100 MHz, $CD_3OD$): $\delta$ 7.35 (s, 5H, arom.); $\delta$ 7.11 (s, 5H, arom.); $\delta$ 5.16 (s, 1H, -C<u>H</u>$NH_2$); $\delta$ 4.99 (s, 1H, -C<u>H</u>NH); IR: $\nu$ 3371 cm$^{-1}$, $\nu$ 3056 cm$^{-1}$, $\nu$ 1685 cm$^{-1}$, $\nu$ 1583 cm$^{-1}$

*2-[(2-amino-2(S)-phenylacetyl)amino]-2(R)-phenylacetic acid **4***

Procedure **D**: 8.47 g **12**

The yield was 1.90 g (40%) after crystallisation. $[\alpha]_D^{20}$ = -21 (c0.3, MeOH); $^1$H-NMR (100 MHz, $CD_3OD$): $\delta$ 7.311 (s, 5H, arom.); $\delta$ 7.09 (s, 5H, arom.); $\delta$ 5.13 (s, 1H, -C<u>H</u>$NH_2$); $\delta$ 5.01 (s, 1H, -C<u>H</u>NH); IR: $\nu$ 3371 cm$^{-1}$, $\nu$ 3033 cm$^{-1}$, $\nu$ 1686 cm$^{-1}$, $\nu$ 1589 cm$^{-1}$; Elemental analysis for $C_{16}H_{16}N_2O_3$: calc.C 67.59%, H 5.67%, N 9.85% found C 65.63%, H 5.70%; N 9.61; MS: ($\frac{m}{z}$) 285 ($M^+$)

*3,6-dimethyl-3,6-diphenyl-2,5-piperazinedione **17***

Heating of **13** at about 150 °C afforded **17** as a white sublimate.

$^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta$ 8.86 (s, 2H, NH); $\delta$ 7.07-6.95 (m, 10H, arom.); $\delta$ 3.30 (s, $H_2O$); $\delta$ 3.28 (s, HDO); $\delta$ 3.30 (s, 6H, $-CH_3$); Elemental analysis for $C_{18}H_{18}N_2O_2$: calc.C 73.45%, H 6.16%, N 9.52% found C 73.34%, H 6.05%; N 9.45; MS: ($\frac{m}{z}$) 294

*e.e. determination of possible guest compounds*

| racemate | method |
|---|---|
| R31 | HPLC, Chiralcel OB |
| R32 | HPLC, Chiralcel OB |
| R35 | GC, β-CD |

For **R8-R27** see chapter 2, section 3.3.2, table 3.3.

## 5.7 References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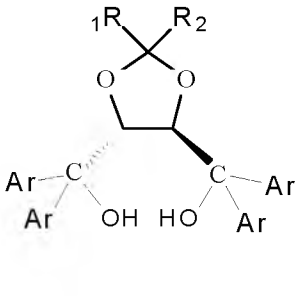
# Summary

Inclusion is a process where two or more compounds crystallise together in a mixed, but regular, crystal lattice. Inclusion resolution is a relatively new way for separating enantiomers from a racemic mixture which employs inclusion with enantiopure compounds as hosts. An enantiopure host compound can lead to chiral recognition, and thus to selective inclusion, of one of the enantiomers of a racemic guest. Thus, it can be used for the resolution of this guest compound in a process which is similar to classical resolution using diastereomeric salts. Inclusion resolution, however, has a number of potential advantages when compared to classical resolution, such as the capability to resolve uncharged compounds and a better potential for the application of asymmetric transformation.

The first successful examples of efficient inclusion resolutions, mostly using Taddols as host compounds (diaryl carbinol derivatives of tartaric acid), were described by *Toda* in the end 80's. Only a limited number of other hosts, such as dipeptides or lactic acid derivatives, have since then been developed and applied in inclusion resolution.

In contrast to classical resolution very little is known about the physico-chemical background, thermodynamics and other fundamental aspects of inclusion resolution. A large part of the study described in this thesis was therefore aimed at elucidating some fundamental aspects of inclusion resolution, especially from a point of view of industrial applicability. Several Taddols and some phenylglycine dipeptides were chosen for a thorough study of fundamental aspects, scope and limitations of inclusion resolution.

Figure 1 shows the twelve different Taddols synthesised and applied in inclusion resolution experiments. The synthesis of these compounds is described in chapter 2.




| | | | |
|---|---|---|---|
| $R_1,R_2$ = -methyl | | $R_1,R_2$ = -cyclohexyl | |
| Ar = -phenyl | **1** | Ar = -phenyl | **9** |
| -*o*-tolyl | **2** | -*p*-tolyl | **10** |
| -*m*-tolyl | **3** | | |
| -*p*-tolyl | **4** | | |
| -*o*-anisyl | **5** | Ar = -*p*-tolyl | |
| -*m*-anisyl | **6** | $R_1,R_2$ = -H | **11** |
| -*p*-anisyl | **7** | $R_1$ = -H, $R_2$ = -phenyl | **12** |
| -*p*-Cl-phenyl | **8** | | |

**Figure 1:** Taddols synthesised and applied in inclusion resolution

Attempts to prepare inclusion complexes with these Taddols and a large selection of guest compounds using different techniques are described in chapter 3. The 30 potential guest compounds were selected from a variety of classes including alcohols, amines, esters, nitriles and acids; most of them are of industrial importance. In total more than 800 inclusion experiments using different methods were performed.

The methods applied were

- with individual Taddols from solution in an appropriate solvent
- with individual Taddols from solution in an appropriate solvent at 15 kbar
- with individual Taddols from solution where the racemic guest compound acts as solvent
- grinding with individual Taddols
- vapour sorption with individual Taddols
- with mixtures of Taddols from solution with appropriate solvent (similar to Dutch Resolution in separation *via* diastereomeric salts)

This ultimately resulted in 38 inclusion complexes (including the successful reproduction of a resolution described by Toda). Only in five cases of inclusion complexes resolution was observed, the other inclusion complexes contained only the racemic guest compounds. Table 1 shows the results of the five new inclusion resolutions found.

| host/guest | chirality guest | *e.e.* | yield | S |
|---|---|---|---|---|
| **2** / lactic acid (2:1) | (*S*) | 71% | 11% | 0.1 |
| **4** / phenylethylamine (1:1) | L | 95% | 41% | 0.8 |
| **4** / *trans*-2-methoxycyclohexanol (2:1) | (*S,S*) | 94% | 39% | 0.8 |
| **9** / 2-amino-1-propanol (1:1) | not det. | 21% | 24% | 0.1 |
| **10** / lactic acid (2:1) | (*S*) | 66% | 19% | 0.2 |

**Table 1:** Inclusion resolution with Taddols

In many cases, obtaining the first batch of crystals seems to constitute the major problem in inclusion crystallisation (the formation of gels and the $^{1}$H-NMR shift experiments indicates strong interactions between many hosts and guests). The problems encountered in the reproduction of some of the inclusion resolutions described in literature may be due to the general problem of obtaining the first crystalline material. The reproduction of inclusion experiments after first crystals are obtained is possible without problems.

The application of mixtures of resolving agents, similar to the very successful Dutch Resolution approach in classical resolution, unexpectedly did not lead to any improvement. The difference in the weak host/guest interactions compared to the strong interaction in salts may be the key factor for this different behaviour.

Taddol **4** has proven to be an especially suitable host for inclusion and resolution of a variety of smaller guest compounds. This compound can include and resolve racemic phenylethylamine with a high efficiency, but it also forms two stable, diastereomeric, inclusion complexes with both pure enantiomers of phenylethylamine. Similar behaviour was observed with *trans*-2-methoxycyclohexanol. Therefore these combinations form suitable model systems for studying physico-chemical aspects of the inclusion resolution process.

Studying the properties of mixtures of diastereomeric inclusion compounds in relation to their different compositions is an essential tool to understand the thermodynamics of the process of

inclusion resolution. The determination of phase diagrams constitutes the first step in obtaining a more detailed knowledge about the subject.

With Taddol **4** being able to include the two enantiomers of phenylethylamine as well as the two enantiomers of *trans*-2-methoxycyclohexanol separately, a description and comparison of both diastereomers of an inclusion compound and the construction of phase diagrams became possible for the first time. These efforts are described in chapter 4.

Initial attempts to construct binary melting phase diagrams failed, since upon heating the inclusion compounds no true melting points are observed, but instead the dissociation of the inclusion compound and evaporation of the guest was observed.

With hexane as solvent, a ternary solution phase diagram was constructed and used to describe the properties of the two Taddol **4** / phenylethylamine diastereomers. The shape of the ternary phase diagram clearly shows solid solution behaviour in respect to the guest compound. That means, the inclusion of both enantiomers of the amine into the chiral cavities formed by Taddol **4** is possible, however, one of them is preferentially included, resulting in an resolution. A single X-ray structure analysis of mixed crystals with equal quantities of the two amine enantiomers clearly showed solid solution of the amine. Amine sites are randomly occupied by D-amine and L-amine.

As previously mentioned, several dipeptides based on phenylglycine have also been applied as potential host compounds in the enantioselective preparation of inclusion complexes (Figure 2). The more than 400 different crystallisation and sorption experiment with these hosts, described in chapter 5, afforded only 4 inclusion resolutions (including the successful reproduction of a resolution described by Akazome). The following table shows the 3 new inclusion resolutions.

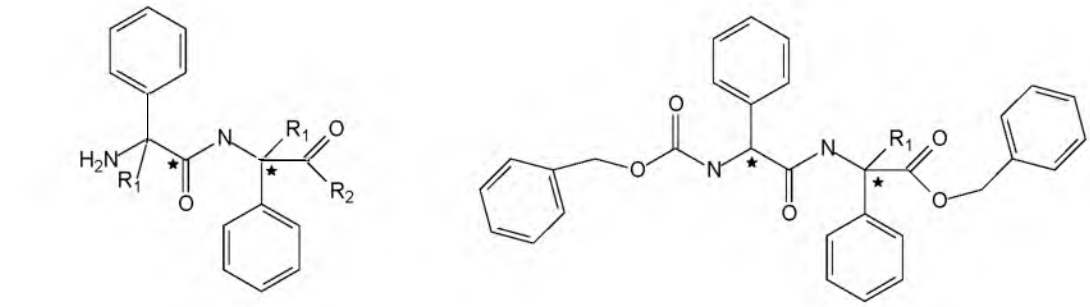



**Figure 2:** Twelve dipeptides based on phenylglycine

| host/guest | chirality guest | e.e. | method |
|---|---|---|---|
| **13** / solketal (1:1) | (*R*) | 48% | sorption |
| **13** / methyl phenyl sulfoxide (1:1) | (*R*) | 36% | sorption |
| **2** / methyl phenyl sulfoxide (1:1) | (*S*) | 73% | sorption |

**Table 2:** Inclusion resolution with dipeptides

Unfortunately, only one new compound, solketal, has been identified to form an inclusion complex with dipeptide kinds of hosts. Its resolution, however, was complicated by the formation of a second polymorphic crystal form of the inclusion compound, which did not show any enantioselectivity.

It became clear in this study that in general the success rate for finding suitable hosts for an application in inclusion resolution is far lower than is the case in classical resolution *via* diastereomeric salts. It is, unfortunately, also much lower than may be expected from studies of the available literature. A further complicating factor is the difficulty of obtaining a first batch of crystals (nucleation problem). The two studied model systems also indicate that solid solution of the guest is common, which will complicate resolution procedures using inclusion compounds.
In summary it must be concluded that, although from an industrial point of view inclusion resolution is highly desirable because of its inherent properties, it seems to be a too random and rare phenomenon for practical applications.

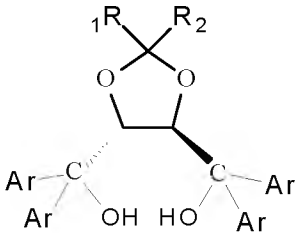
# Samenvatting

Insluiting is een proces waarbij twee of meer verbindingen samen in een gemengd, maar regelmatig, kristalrooster uitkristalliseren. Inclusie resolutie is een relatief nieuwe methode voor enantiomerenscheiding die gebruik maakt van insluiting met enantiomeer zuivere gastheren. Het gebruik van een enantiomeer zuivere gastheer kan leiden tot chirale herkenning, en zodoende tot selectieve insluiting, van één van de enantiomeren van een racemische gast. Hierdoor kan dit toegepast worden voor de enantiomerenscheiding van deze gast in een proces dat vergelijkbaar is met klassieke resolutie gebruik makend van diastereomere zouten. Inclusie resolutie heeft echter vergeleken met klassieke resolutie een aantal potentiële voordelen, zoals de mogelijkheid om ongeladen verbindingen te splitsen en betere mogelijkheden voor de toepassing van asymmetrische transformatie.

De eerste succesvolle voorbeelden van efficiënte inclusie resoluties, met name gebruik makend van Taddolen as gastheer moleculen (diaryl carbinol derivaten van wijnsteenzuur), zijn beschreven door Toda *et al.* aan het eind van de jaren 80. Slechts een beperkt aantal gastheren, zoals dipeptides en enkele melkzuur derivaten, is daarna nog ontwikkeld en toegepast in inclusie resoluties.

In tegenstelling tot klassieke resolutie is slechts weinig bekend over de fysisch-chemische achtergronden, thermodynamica en andere fundamentele aspecten van inclusie resolutie. Een groot deel van het onderzoek beschreven in dit proefschrift was daarom gericht op het ophelderen van sommige van deze fundamentele aspecten, met name vanuit het oogpunt van mogelijke industriële toepasbaarheid. Een aantal Taddolen en enkele phenylglycine dipeptide derivaten werden geselecteerd voor een grondige bestudering van fundamentele aspecten, mogelijkheden en beperkingen van inclusie resoluties.

Figuur 1 laat de twaalf Taddolen zien die gesynthetiseerd en vervolgens toegepast werden in inclusie resolutie experimenten. De synthese van deze verbindingen is beschreven in hoofdstuk 2.




| | | | |
|---|---|---|---|
| $R_1,R_2$ = -methyl | | $R_1,R_2$ = -cyclohexyl | |
| Ar = -phenyl | **1** | Ar = -phenyl | **9** |
| -*o*-tolyl | **2** | -*p*-tolyl | **10** |
| -*m*-tolyl | **3** | | |
| -*p*-tolyl | **4** | | |
| -*o*-anisyl | **5** | Ar = -*p*-tolyl | |
| -*m*-anisyl | **6** | $R_1,R_2$ = -H | **11** |
| -*p*-anisyl | **7** | $R_1$ = -H, $R_2$ = -phenyl | **12** |
| -*p*-Cl-phenyl | **8** | | |

**Figuur 1:** Taddolen gesynthetiseerd en toegepast in inclusie resolutie

De pogingen om insluitverbindingen te vormen, met deze Taddolen als gastheermoleculen en met een uitgebreide selectie van gastmoleculen onder toepassing van verschillende technieken, zijn beschreven in hoofdstuk 3. De 30 geteste potentiële gastmoleculen werden geselecteerd uit diverse klassen van verbindingen, zoals alcoholen, amines, esters, nitrillen en

carbonzuren; de meeste hiervan zijn van industrieël belang. In totaal werden meer dan 800 verschillende insluit experimenten uitgevoerd gebruik makend van diverse methodes. Toegepaste methodes waren:

- met een enkelvoudig Taddol uit een oplossing met geschikt oplosmiddel
- met een enkelvoudig Taddol uit een oplossing met geschikt oplosmiddel bij een druk van 15 kBar
- met een enkelvoudig Taddol uit een oplossing waarbij overmaat gast als oplosmiddel dienst doet
- droog vermalen van een mengsel van Taddol en gast
- adsorptie van gast uit de gasfase door een enkelvoudig Taddol
- met mengsels van Taddolen uit een oplossing (vergelijkbaar met "Dutch Resolution" bij de scheiding van diastereomere zouten)

Dit resulteerde uiteindelijk in 38 insluitverbindingen (inclusief het succesvol reproduceren van een door Toda et al. beschreven splitsing). Echter slechts in 5 gevallen werd ook resolutie van de gast waargenomen, in de andere insluitverbindingen werd de gast als racemaat ingesloten. Tabel 1 laat de resultaten van de 5 nieuw gevonden inclusie resoluties zien

| gastheer /gast | chiraliteit guest | *e.e.* | opbrengst | S |
|---|---|---|---|---|
| **2** / melkzuur (2:1) | (*S*) | 71% | 11% | 0.1 |
| **4** / fenylethylamine (1:1) | L | 95% | 41% | 0.8 |
| **4** / *trans*-2-methoxycyclohexanol (2:1) | (*S,S*) | 94% | 39% | 0.8 |
| **9** / 2-amino-1-propanol (1:1) | not det. | 21% | 24% | 0.1 |
| **10** / melkzuur (2:1) | (*S*) | 66% | 19% | 0.2 |

**Tabel 1:** Inclusie resolutie met Taddolen

Het lijkt er op dat in veel gevallen het verkrijgen van de eerste portie insluit kristallen een groot probleem vormt bij inclusie resolutie (de vorming van gels en $^{1}$H-NMR shift experimenten wijzen op sterke interacties tussen veel van de gasten en gastheren). De problemen die ondervonden werden bij pogingen om in de literatuur beschreven inclusie resoluties te reproduceren kunnen mogelijk ook toegeschreven worden aan het algemene probleem om een eerste portie kristallijn materiaal te verkrijgen. Het reproduceren van een inclusie resolutie nadat eerste kristallen beschikbaar zijn vormt geen enkel probleem.

De toepassing van mengsels van splitsingsmiddelen, vergelijkbaar met de zeer succesvolle "Dutch Resolution" benadering in klassieke resolutie *via* diastereomere zouten, gaf tegen alle verwachtingen in geen verbeteringen. Het verschil tussen de relatief zwakke (H-brug en van der Waals) gast/gastheer interacties in inclusieverbindingen vergeleken met de sterke ionogene interacties in zouten, zal waarschijnlijk een sleutelrol spelen bij dit verschil in gedrag.

Het is aangetoond dat Taddol **4** een bijzonder geschikte gastheer is voor de insluiting en splitsing van een groot aantal kleinere gastmoleculen. Deze verbinding is in staat om racemisch fenylethylamine met hoge efficiëntie in te sluiten en te splitsen, maar vormt daarnaast ook twee stabiele, diastereomere, inclusieverbindingen met beide zuivere enantiomeren van fenylethylamine. Soortgelijk gedrag werd ook gevonden met *trans*-2-methoxycyclohexanol. Daarom vormen deze combinaties geschikte modelsystemen voor de bestudering van fysisch-chemische aspecten van het inclusie resolutie proces.

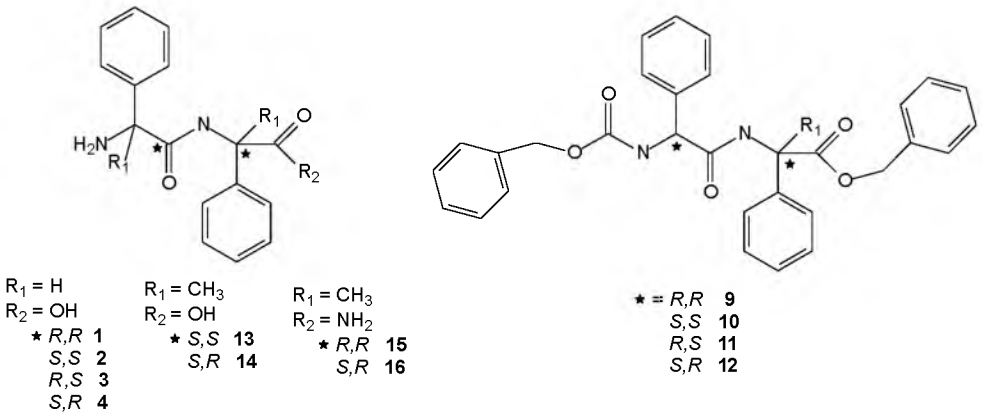
Bestuderen van de eigenschappen van mengsels van diastereomere inclusie verbindingen in relatie tot de verschillende samenstellingen is een essentiële stap om een begrip te krijgen van de thermodynamica van inclusie resolutie. Het bepalen van fasediagrammen vormt de eerste stap in het verkrijgen van een meer gedetailleerd inzicht in dit onderwerp.

Daar Taddol **4** in staat is om zowel de twee enantiomeren van phenylethylamine als de twee enantiomeren van *trans*-2-methoxycyclohexanol elk afzonderlijk in te sluiten, is het hiermee voor het eerst mogelijk om beide diastereomeren van een inclusieverbinding te bestuderen, te vergelijken en een fasediagram op te stellen. Dit wordt beschreven in hoofdstuk 4 van dit proefschrift.

Initiële pogingen om een binair smeltpunts fasediagram op te stellen waren niet succesvol aangezien de gebruikte diastereomere inclusieverbindingen geen normaal smeltpunt lieten zien, maar in plaats daarvan dissociatie van de inclusieverbinding en de verdamping van de gast te zien gaven.

Met hexaan als oplosmiddel was het wel mogelijk een ternair oplossings fasediagram te construeren van de twee Taddol **4** / phenylethylamine diastereomeren en hiermee de eigenschappen van deze twee verbindingen te beschrijven. De vorm van het ternaire fasediagram laat duidelijk mengbaarheid in de vaste fase zien van de gast. Dit betekend dat beide enantiomeren van het amine in de chirale holtes gevormd door Taddol **4** ingesloten kunnen worden, maar dat er een duidelijke voorkeur voor één van beide bestaat wat resulteert in een gedeeltelijke resolutie. Een éénkristal röntgen analyse van een gemengd kristal met gelijke hoeveelheden van beide enantiomeren ingesloten laat duidelijk een willekeurige verdeling van de twee enantiomeren van het amine in het kristal zien.

Zoals al eerder werd opgemerkt zijn ook diverse dipeptides, gebaseerd op phenylglycine, toegepast als potentiële gastheer verbindingen voor de enantioselectieve bereiding van insluitverbindingen (Figuur 2). De meer dan 400 verschillende kristallisatie en sorptie experimenten met deze gastheren, beschreven in hoofdstuk 5, leverden slechts 4 inclusie resoluties op (inclusief de reproductie van een door Akazome beschreven resolutie). Tabel 2 laat de resultaten van de drie nieuwe resoluties zien.




**Figuur 2:** 12 dipeptides gebaseerd op fenylglycine

| gastheer/gast | chiraliteit guest | e.e. | methode |
|---|---|---|---|
| **13** / solketal (1:1) | (*R*) | 48% | sorption |
| **13** / methylphenylsulfoxide (1:1) | (*R*) | 36% | sorption |
| **2** / methylphenylsulfoxide (1:1) | (*S*) | 73% | sorption |

**Tabel 2:** Inclusie resoluties met dipeptides

Helaas werd slechts één nieuwe gast gevonden: solketal, welke een insluitverbinding vormt met de dipeptide gastheren. De resolutie van deze verbinding werd echter nog verder gecompliceerd door de vorming van een tweede polymorfe kristalvorm van de inclusieverbinding, welke geen enantioselectiviteit.liet zien.

Het is in dit onderzoek duidelijk geworden dat in het algemeen het succes percentage bij het zoeken naar een geschikte gastheer voor een inclusie resolutie veel geringer is dan bij klassieke resolutie met behulp van diastereomere zouten. Dit percentage is helaas ook veel lager dan verwacht werd op grond van de beschikbare literatuur. Een verdere complicatie is het verkrijgen van de eerste kristallen van een inclusie verbinding (het nucleatieprobleem). De twee bestudeerde modelsystemen vormen verder een aanwijzing dat menging van de twee enantiomeren van de gast in de kristallijne fase een algemeen voorkomend verschijnsel is. Dit zal resolutie *via* inclusie verbindingen nog verder compliceren.

Samenvattend moet geconcludeerd worden dat vanuit een industrieel gezichtspunt inclusie resolutie weliswaar zeer aantrekkelijk is vanwege enkele inherente voordelen, maar dat het een te zeldzaam en willekeurig fenomeen is voor praktische toepassingen.

# Publications/Presentations

S. Müller, C. Afraz, A. Bruggink und G. Ariaans *„Separation of enantiomers by formation of inclusion compounds and study of the physical chemistry involved“, presentation,* University of Nijmegen, The Netherlands, March 2000

S. Müller, A. Bruggink und G. Ariaans *„Separation of enantiomers using crystalline inclusion compounds“, presentation,* SYNCOM, Groningen, The Netherlands, October 2000

S. Müller, A. Bruggink und G. Ariaans *„The physical chemistry of inclusion resolution*“, presentation, Dutch Resolution, NWO-Meeting, Groningen, The Netherlands, December 2000

S. Müller, A. Bruggink und G. Ariaans *“New resolving agents based on dipeptides in inclusion resolution“, presentation,* NWO-Meeting, Geleen, The Netherlands, December 2001

S. Müller, A. Bruggink und G. Ariaans *“Inclusion resolution with Taddols and dipeptide hosts“, presentation,* NWO-Meeting, Groningen, The Netherlands, June 2002

S. Müller, A. Bruggink, G. Ariaans, B. Kaptein, Q. Broxterman *“First phase diagrams of a pair of diastereomeric inclusion compounds“,* poster, 14th ISCD Kongress, Hamburg, Germany, September 2002

S. Müller, A. Bruggink and G. Ariaans *“Dipeptides, suitable hosts in inclusion resolution?“,* presentation, NWO-Meeting, Nijmegen, The Netherlands, December 2002

S. Müller, A. Bruggink, G. Ariaans, B. Kaptein, Q. Broxterman *“First phase diagrams of a pair of diastereomeric inclusion complexes“,* publication, in preparation

S. Müller, M.C. Afraz, A. Bruggink, G. Ariaans, B. Kaptein, Q. Broxterman *“Scope and limitations of inclusion resolutions“,* publication, in preparation

S. Müller, A. Bruggink, G. Ariaans, B. Kaptein, Q. Broxterman *“Inclusion resolution with dipeptide hosts“,* publication, in preparation

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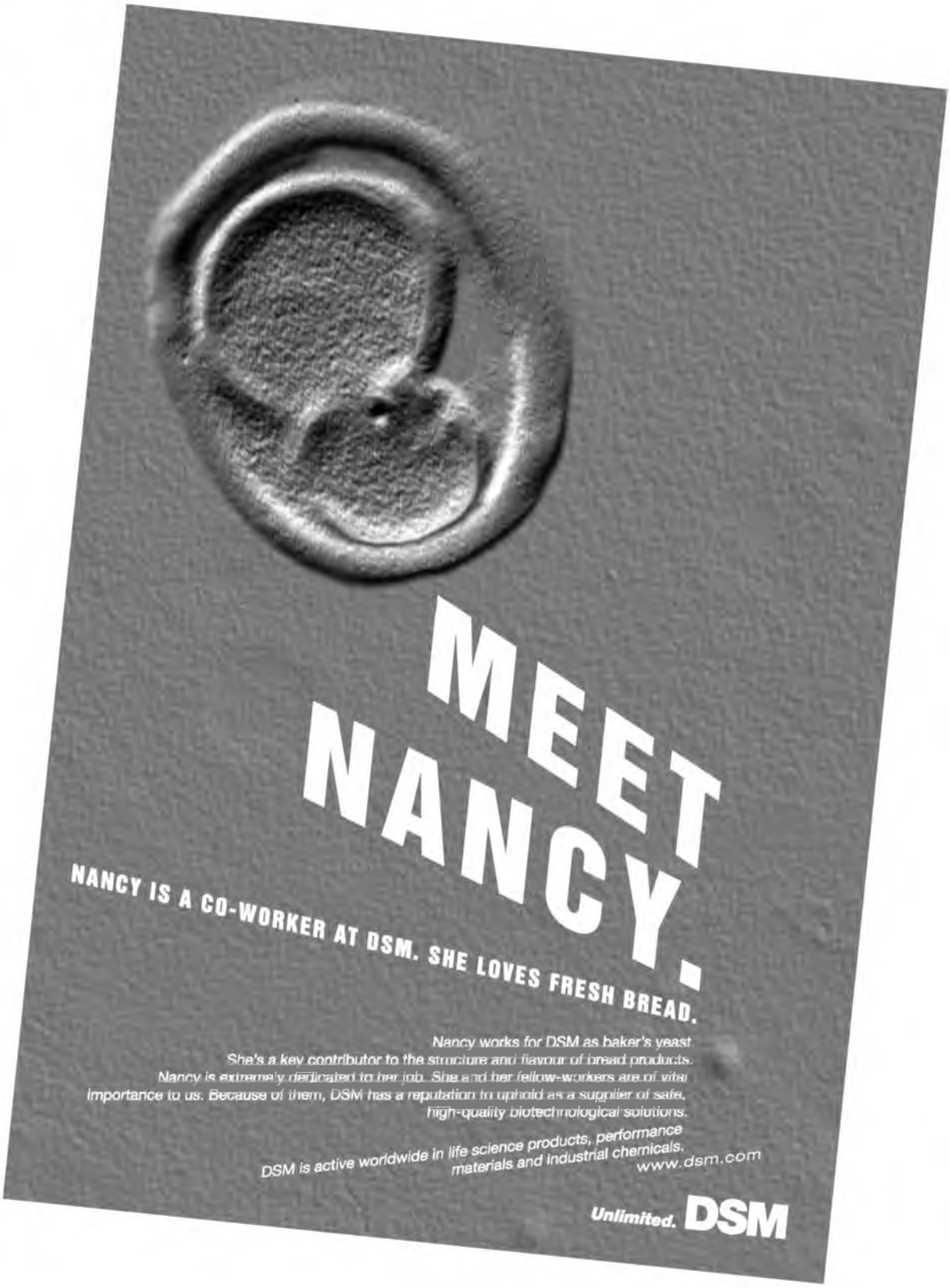
# Curriculum Vitae

Simona Müller was born in Sevelen (Germany) on 13th August 1971. In 1990 she graduated with the German *Abitur* at the Grammar School, Städtisches Gymnasium Kamp-Lintfort.
In the same year, she started the university program of chemistry at the Gerhard Mercator University of Duisburg. From 1996-1997 she participated in two foreign undergraduate research projects at the Catholic University of Nijmegen, The Netherlands; one in the Department of Organic Chemistry in the group of Prof. dr. B. Zwanenburg and one in the Department of Inorganic Chemistry in the group of Prof. dr. A. Gal.
After her return to Germany, she passed the final exams in Theoretical-, Physical-, Organic and Inorganic Chemistry and was awarded the M.Sc. in Chemistry, the German *Diplom-Chemikerin* degree in 1998. Her final graduation research project was performed in the Department of Industrial Organic Chemistry in the group of Prof. dr. A. Bruggink and Prof. dr. B. Zwanenburg in co-operation with Prof. dr. D. Döpp of the Gerhard Mercator University of Duisburg, Germany.
Since 1999 she worked as Ph.D. student (AIO) at the NSR Center for Molecular Structure, Design and Synthesis in the Department of Industrial Organic Chemistry under the supervision of Prof. dr. A. Bruggink (Nijmegen University and DSM-Research), Dr. G.J.A. Ariaans (Nijmegen University and Synthon BV) and Prof. dr. B. Zwanenburg, University of Nijmegen, The Netherlands. During the Ph.D. phase she gave supervision to students. She participated in several courses in Economics and Law at the Fernuniversität of Hagen, Germany.


MEET NANCY.
NANCY IS A CO-WORKER AT DSM. SHE LOVES FRESH BREAD.
Nancy works for DSM as baker's yeast.
She's a key contributor to the structure and flavour of bread products.
Nancy is extremely dedicated to her job. She and her fellow-workers are of vital
importance to us. Because of them, DSM has a reputation to uphold as a supplier of safe,
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